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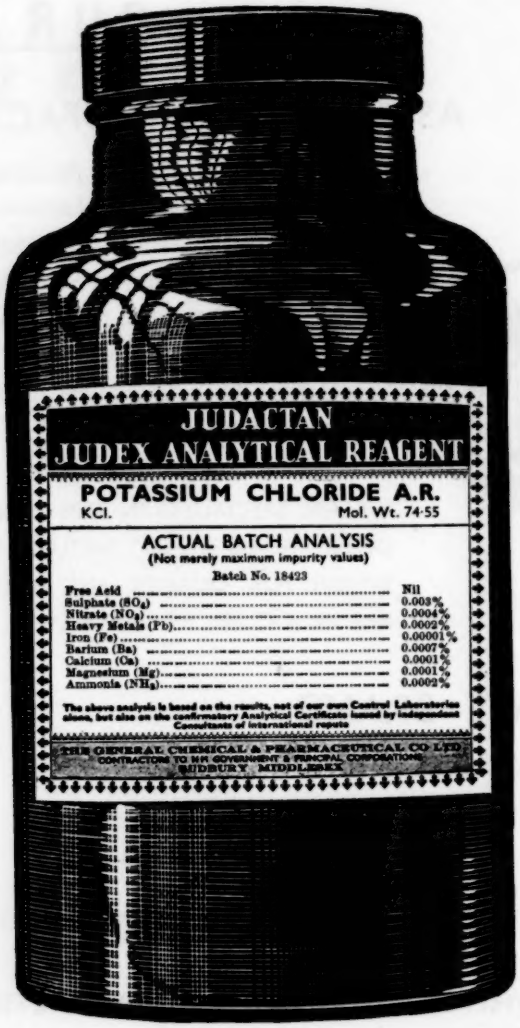
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640. *The Kinetics and Mechanism of Nucleophilic Displacements in Allylic Systems. Part I. Reaction of 3 : 3-Dichloroprop-1-ene with the Ethoxide Ion.*

By P. B. D. de la Mare and C. A. Vernon.

3 : 3-Dichloroprop-1-ene reacts with sodium ethoxide in ethyl alcohol to give, as main products, (i) acraldehyde diethylacetal and (ii) *cis*- and *trans*-1-chloro-3-ethoxyprop-1-ene. The kinetics of these processes, which contribute nearly equally to the total reaction, have now been investigated separately, and have both been shown to be of the kinetic form $-d[RCl_2]/dt = k[RCl_2][OEt^-]$. The latter reaction is interpreted as a synchronous bimolecular substitution with anionotropic rearrangement (S_N2'), and the effect of structure on the rate of such reactions is briefly discussed.

3 : 3-Dichloroprop-1-ene ("acraldehyde dichloride"), on reaction with nucleophilic reagents, gives derivatives of its isomer, 1 : 3-dichloropropene. The literature concerning these substitutions accompanied by anionotropic rearrangement is summarised by Huntress ("Organic Chlorine Compounds," John Wiley and Sons, New York, 1948, p. 604). Typically, it was observed by Kirrman, Pacaud, and Dosque (*Bull. Soc. chim.*, 1934, **1**, 860) that, after refluxing 3 : 3-dichloroprop-1-ene with ethyl-alcoholic sodium ethoxide for 15 hours, the products of reaction contain a little of an unidentified propargyl derivative, together with 1-chloro-3-ethoxyprop-1-ene, characterised by its density and refractive index.

This reaction has recently been studied kinetically by Andrews and Kepner (*J. Amer. Chem. Soc.*, 1948, **70**, 3456) and by Smith and King (*ibid.*, 1950, **72**, 95). Their observation, that only part of the chlorine present in the compound is released in the stage which determines the measured rate of the reaction, suggests again that a rearranged material forms at least part of the product.* The bearing of this observation on the mechanism of the reaction was not, however, discussed by either of these groups of workers, although they reported that the reaction was bimolecular, and considerably slower than the corresponding reactions of the isomeric *cis*- and *trans*-1 : 3-dichloropropenes.

Many anionotropic changes are believed to be unimolecular substitutions (S_N1',) in which ionisation of the halide forms a mesomeric cation, which may then react with a nucleophilic reagent in either of two positions. Catchpole, Hughes, and Ingold (*J.*, 1948, 8) have modified and amplified the account of such processes given by Burton and Ingold (*J.*, 1928, 904). The corresponding bimolecular mechanism, involving rearrangement synchronous with bimolecular displacement of halide ions (S_N2'), was discussed first by Hughes (*Trans. Faraday Soc.*, 1938, **34**, 185), but the experimental realisation of this possibility has proved somewhat elusive. The first conclusive demonstration of such a reaction mechanism was given by England and Hughes (*Nature*, 1951, **168**, 1002). It has hence become apparent, as was discussed also by Hughes and Ingold (*J. Chim. phys.*, 1948, **45**, 241), that direct bimolecular substitution (S_N2) is often preferred to substitution with rearrangement (S_N2') by a factor which is sufficiently large to prevent the product of the latter reaction from being easily detected.

It is well known that *gem*-dihalides are rather resistant to bimolecular nucleophilic substitution. For instance, with alcoholic potassium hydroxide, methylene chloride reacts less rapidly than methyl chloride (Petrenko-Kritschenko and Opotzsky, *Ber.*, 1926, **59**, 2131), and methylene bromide exchanges with bromide ions 50 times less rapidly than does ethyl bromide (de la Mare, Hughes, and Ingold, unpublished work). For this reason, it seemed likely that the bimolecular reactions of 3 : 3-dichloroprop-1-ene would occur less readily than those of allyl chloride. The corresponding S_N2' substitutions with rearrangement should, however, be favoured, seeing that the electron-withdrawing character

* Direct nucleophilic displacement of chlorine would produce an α-chloro-ether, and such substances characteristically lose chlorine with great rapidity in alkaline solution.

of the $CHCl_2$ group must, by its inductive effect, reduce the density of unsaturation electrons on the 1-carbon atom, and thus render the latter more vulnerable (cf. Hughes and Ingold, *loc. cit.*) to attack by nucleophilic reagents. Taking into account these theoretical considerations, together with the established facts that the reaction with alcoholic sodium ethoxide (*a*) gave the rearranged ether and (*b*) appeared to be bimolecular, we decided to reinvestigate these aspects in some detail, in the hope of demonstrating an S_N2' attack by ethoxide ions.

Experimental

(*a*) *Materials and Methods.*—3 : 3-Dichloroprop-1-ene was prepared essentially by King and Smith's method (*J. Amer. Chem. Soc.*, 1950, **72**, 3459). The product, after fractionation through a helix-packed column, had b. p. 84·0—84·8°/766 mm., n_D^{25} 1·4456 (Found: C, 32·2; H, 3·7. Calc. for $C_3H_4Cl_2$: C, 32·4; H, 3·6%). After oxidation with potassium permanganate in acetone, there was recovered from the acidic products, dichloroacetic acid, identified as its *S*-benzylthiuronium derivative, m. p. 173—174°, not changed on admixture with an authentic sample.

cis- and *trans*-1 : 3-Dichloropropene were prepared from a commercial sample of the di- and tri-chloropropenes (" Shell DD Soil Fumigant "). This was carefully fractionated, first at atmospheric pressure and then at reduced pressure, giving products with the following constants (*cis*-isomer listed first), which agree well with those recorded by King and Smith (*loc. cit.*), as well as by Hatch, Gordon, and Rust (*J. Amer. Chem. Soc.*, 1948, **70**, 1003): b. p. 103—104°, 110—112°/760 mm.; 50·3—50·7°/111 mm., 62—63°/136 mm.; n_D^{25} 1·4657, 1·4722. Both these compounds appeared to be substantially free from other isomers, the reactivities of which are considerably different (cf. Smith and King, *loc. cit.*).

cis- and *trans*-1-Chloro-3-ethoxyprop-1-ene were prepared by the action of alcoholic sodium ethoxide on the corresponding dichloropropenes, as described by Smith and King (*loc. cit.*). The samples appeared kinetically to be about 97% pure, and had the following constants (*cis*-isomer listed first): b. p. 64·1—64·6°, 70—71°/102 mm.; n_D^{25} 1·4288, 1·4311 (Found: C, 50·4, 50·3; H, 7·4, 7·5; Cl, 29·7, 29·5. Calc. for C_5H_9OCl: C, 49·8; H, 7·5; Cl, 29·4%).

Hall and Stern (*Chem. and Ind.*, 1950, 775) have shown that the material described as " acrolein diethyl acetal " by Pingert (*Org. Synth.*, **26**, 1) is really 3-ethoxypropaldehyde. We are grateful to these authors, and to the Distillers Co. Ltd., Great Burgh, Epsom, Surrey, for a genuine sample of acraldehyde diethyl acetal, prepared by Fischer and Baer's method (*Helv. Chim. Acta*, 1935, **18**, 514), b. p. 59°/76 mm., n_D^{20} 1·4011, n_D^{25} 1·3990.

Thermostats were of conventional design. Portions of the reaction mixture were sealed in bulbs leaving little dead space, and removed from the thermostat at appropriate intervals for titration either acidimetrically, or potentiometrically with silver nitrate solution. The initial concentrations of organic chloride were determined by weight, and those of alkali by titration with standard acid. Blank determinations were used to allow for reaction during the period of warming to thermostat temperature.

The following are details of a measurement of the rate of reaction of *cis*-1-chloro-3-ethoxyprop-1-ene (0·0465M) with sodium ethoxide (0·515M) in dry ethyl alcohol at 63·7°. Samples (5·53 ml.) were titrated potentiometrically with silver nitrate solution (0·0100M):

Time (min.)	0	42	86	153	299	417	1395	1870	3270	∞
Titre (ml. of $AgNO_3$) ...	0·52	0·85	1·14	1·65	2·75	3·50	9·20	11·10	16·10	26·25
10^4k_2 *	—	6·40	5·79	6·06	6·21	6·06	6·13	5·98	6·08	—

Mean values at other temperatures † are: 44·6°, $4·3 \times 10^{-5}$; 85·7°, $9·5 \times 10^{-3}$; 100·0°, $4·28 \times 10^{-2}$.

* All values of k_2 quoted in this paper have been calculated by the formula $k_2 = 2·303/t[\mathrm{NaOEt}]) . \log_{10}\{(a_\infty - a_0)/(a_t - a_0)\}$, where a_t is the titre at time t minutes; this is appropriate for second-order reactions, such as these, in which the concentration of sodium ethoxide is much greater than that of the organic halide. The quoted values of a_∞ were determined experimentally. The units of k_2 are l. g.-mol.$^{-1}$ min.$^{-1}$.

† The abnormal values for the Arrhenius parameters ($B = 10^{17}$ l. g.-mol.$^{-1}$ min.$^{-1}$, $E = 31$ kcals.), and the stereospecificity of this reaction, in which the *cis*-isomer reacts several thousand times more rapidly than the *trans*-compound, will be discussed in future communications.

(*b*) *Products of the Reaction of* 3 : 3-*Dichloroprop*-1-*ene.*—3 : 3-Dichloroprop-1-ene (23 g.) was allowed to react for 17 days at 44·6° with 200 ml. of 1·3M-sodium ethoxide in dry ethyl

alcohol. Subsidiary experiments showed that, in this time, 49% of the theoretical amount of chlorine would have been liberated, whereas, in the absence of alkali, less than 0·5% of solvolysis would have occurred. The product was added to 500 ml. of 2N-hydrochloric acid, and extracted with pentane. The pentane extract was washed with water, dried, and fractionated, yielding 2·3 g., b. p. 120—128°, n_D^{25} 1·4280. This had the properties of a mixture of the 1-chloro-3-ethoxyprop-1-enes (Found: C, 49·4; H, 7·4. Calc. for C_5H_9OCl: C, 49·8; H, 7·5%), as was confirmed kinetically in the following way. At 85·7°, the reaction of the *trans*-isomer with 0·5N-sodium ethoxide in ethyl alcohol is negligibly slow, whereas more than 99% of the *cis*-isomer is destroyed in 1500 minutes. The following illustrates the rate of development of chloride ion from a solution of the above material (0·0766M, calculated as 1-chloro-3-ethoxyprop-1-ene) with sodium ethoxide (0·5076M) in ethanol at 85·7°:

Time (min.)	0	68	123	214	312	403	∞
Titre (ml. of 0·0100M-$AgNO_3$)	1·28	3·60	5·12	6·88	8·30	9·08	11·08
k_2	—	0·0085	0·0087	0·0085	0·0087	0·0086	—

The further rate of development of chloride ion was then measured at 120°, at which temperature all the *cis*-isomer is destroyed in the time allowed for warming to thermostat temperature, as follows:

Time (hours)	0	21·9	71·7	92·7	117·7	143·2	164·5	186·6	∞
Titre (ml. of 0·0100M-$AgNO_3$)	12·03	15·38	20·93	22·71	24·95	27·00	28·22	29·49	44·56
10^4k_2	—	1·99	1·79	1·74	1·75	1·75	1·70	1·69	—

The mean rate coefficients thus determined (*cis*-isomer, 0·0086 at 85·6°; *trans*-isomer, 0·000177 at 120°) agree well with those determined independently for pure specimens of these compounds (*cis*-isomer, 0·0095 at 85·7°; *trans*-isomer, 0·000173 at 120°). This product thus contains 25% of the *cis*- and 75% of the *trans*-isomer.

The relatively fast rate of elimination of hydrogen chloride from *cis*-1-chloro-3-ethoxyprop-1-ene made it unlikely that it would be possible to obtain a quantitative estimate of the amount formed in the reaction, or to obtain it in a pure state except by use of prohibitively large quantities of material. In the following experiment, 63·5 g. of 3:3-dichloroprop-1-ene were allowed to react to completion (10 days) with 1400 ml. of 1·8N-sodium ethoxide. The product was extracted with pentane from the alkaline solution after dilution with water, dried, and fractionated, giving the following fractions:

Fraction	B. p./mm.	Wt. (g.)	n_D^{25}	Fraction	B. p./mm.	Wt. (g.)	n_D^{25}
1	74—78°/760	3·0	1·4050	7	59—61/67	4·2	1·4163
2	54—56/67	2·4	1·4009	8	61—63/67	2·6	1·4232
3	56—57·5/67	5·2	1·3995	9	63—64/67	2·4	1·4250
4	57·5/67	4·9	1·4007	10	64—70/67	2·6	1·4220
5	57·5—58·5/67	4·5	1·4025	11	Residue of higher b. p.	5·8	—
6	58·5—59/67	2·2	1·4070				

The first fraction may have contained propargyl ether, which has n_D^{25} 1·3995, b. p. 82·5°/760 mm., but we were unable to isolate a pure specimen. Fraction 3 was nearly pure acraldehyde diethyl acetal, n_D^{25} 1·3992 (Found: C, 64·6; H, 10·8. Calc. for $C_7H_{14}O_2$: C, 64·8; H, 10·7%). It gave the same colour (within 5%) as an authentic sample, when treated with tryptophan and hydrochloric acid under the conditions of the analytical determination of acraldehyde described below.

Fractions 5—9 contained increasing amounts of *trans*-1-chloro-3-ethoxyprop-1-ene, as judged from the refractive indices. These, together with fraction 10, were treated with 15 ml. of ethanol and 150 ml. of 2N-hydrochloric acid. After 2 hours, the product was extracted with pentane, and the extract was washed with saturated sodium hydrogen sulphite, then with water, dried, and fractionated, giving 6 g., which were steam-distilled with N-hydrochloric acid. The product was dried and fractionated, giving a fraction of n_D^{25} 1·4298 (Found: C, 50·2; H, 8·0. Calc. for C_5H_9OCl: C, 49·8; H, 7·5%).

The fractions of higher b. p. (fractions 10 and 11) were complex, and similar to those produced by the action of sodium ethoxide on *cis*-1-chloro-3-ethoxyprop-1-ene. It appears that elimination from this compound is followed by polymerisation or condensation with other materials present in the solution. No pure fraction was obtained, the b. p. at atmospheric pressure rising steadily to >220°, and this material was not investigated further.

In order to demonstrate that, from incomplete reaction with sodium ethoxide, unchanged 3 : 3-dichloroprop-1-ene can be recovered, 40 g. of this substance were treated with excess of 0·98N-sodium ethoxide at 85·4° for a time sufficient to allow *ca.* 35% release of chlorine from the compound. There was recovered in the usual way *ca.* 5 g., b. p. 83—83·6°, n_D^{25} 1·4439 (Calc. 1·4456) (Found: C, 34·3; H, 3·8. Calc. for $C_3H_4Cl_2$: C, 32·4; H, 3·6%), and hence it seems probable that the product is an azeotrope containing about 10% of 1-chloro-3-ethoxyprop-1-ene, as would agree both with the analytical data and with the refractive index. The following experiment shows the rate of solvolysis of this substance in 50% alcohol–water at 85·5°, 5·53-ml. portions being titrated with alkali:

Time (min.)	0	6	15	24	32	48	62	110	172	∞
Titre (ml. of 0·01996N-alkali)	1·79	2·60	3·81	4·89	5·85	7·45	8·80	11·90	14·49	17·41
10^3k_1 *	—	8·9	9·2	9·2	9·4	9·4	9·6	9·5	9·8	—

* Values of k_1 have been calculated by using the formula $k_1 = (2{\cdot}303/t) \log_{10} (a_\infty - a_0)/(a_t - a_0)$, where a_t is the titre at time t minutes, and are given in units min.$^{-1}$.

Authentic 3 : 3-dichloroprop-1-ene reacted at an almost identical rate; herewith are the data at 85·3°:

Time (min.)	0	6	12	18	24	32
Titre (ml. of 0·01788N-alkali)	1·98	3·11	3·99	4·98	5·85	6·75
10^3k_1	—	9·9	9·0	9·2	9·2	8·7

Time (min.)	41	47	57	131	183	∞
Titre (ml. of 0·01788N-alkali)	8·12	8·82	9·91	15·63	17·90	21·60
10^3k_1	9·2	9·2	9·1	9·1	9·1	—

It is certain, therefore, that the product recovered in this experiment was substantially the unchanged starting material.

(*c*) *Kinetics of the Reaction of* 3 : 3-*Dichloroprop*-1-*ene.*—(i) *Rate of formation of acraldehyde diethylacetal.* Many of the recorded methods for the detection and estimation of acraldehyde are not specific. Circle, Stace, and Boruff (*Ind. Eng. Chem. Anal.*, 1945, **17**, 259) have, however, recently developed a method, involving condensation with tryptophan in acid solution, suitable for the colorimetric estimation of this substance, acetaldehyde and other common aldehydes giving no interfering colour. The following procedure, which is substantially that recommended by the above workers, was therefore adopted. A sample (2 ml., in alcohol, containing less than 0·01M-acraldehyde diethyl acetal) was added to 3 ml. of tryptophan solution (0·7 g./l. in 0·02N-HCl). Ice-cold, 12N-hydrochloric acid (10 ml.) was added, the colour was allowed to develop for 2 hours in the dark at room temperature, and its intensity then measured in a 1-cm. cell in a Hilger Spekker absorptiometer, with a yellow-green filter No. 605, and compared with the colour obtained from a standard alcoholic solution of acraldehyde diethylacetal. This substance is rapidly hydrolysed to acraldehyde under the conditions of measurement, and in our hands gave a colour slightly more intense (by about 10%) than that given by commercial samples of acraldehyde treated in similar fashion.

Neither 3 : 3-dichloroprop-1-ene nor the 1-chloro-3-ethoxyprop-1-enes gave any colour with the reagent or disturbed the development of colour. It was found, however, that the complex products obtained by the prolonged action of sodium ethoxide on *cis*-1-chloro-3-ethoxyprop-1-ene interfered slightly with the infinity determinations. The following experiment shows the rate of development of chloride and of material analysing as acraldehyde from *cis*-1-chloro-3-ethoxyprop-1-ene (0·0525M) and sodium ethoxide (0·617M) in alcohol at 100°, the initial tube being taken after a warming-up time of 10 minutes:

Time (min.)	0	8	12	18	23	28	90	213	∞
Chloride (%)	23·1	36·3	42·8	50·9	56·1	61·2	89·8	98·3	100
" Acraldehyde " (%)	0·0	0·0	0·0	0·0	0·0	0·0	4·3	18·4	38·4

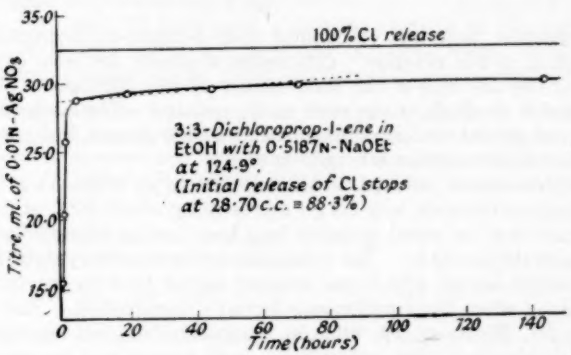
It is clear that the interference becomes important only towards the end of the reaction, and hence the infinity determinations for the corresponding reaction of 3 : 3-dichloroprop-1-ene have been corrected slightly (≯10%) to allow for this disturbance. The following shows the rate of production of acraldehyde diethylacetal from 0·0514M-3 : 3-dichloroprop-1-ene and 0·549M-sodium ethoxide in alcohol at 24·9°. The initial tube was taken after a warming-up time of 20 minutes:

Time (min.)	0	177	239	310	377	826	1068	2278	∞ (obs.)	∞ (corr.)
Spekker reading ...	0·103	0·186	0·363	0·409	0·474	0·850	1·027	1·680 †	2·824 †	2·589
10^4k_2 *	—	8·43	8·66	8·11	8·12	8·28	8·31	8·44	—	—

* These values of k_2 have been calculated as previously described, Spekker readings being used in place of titres. The observed infinity value was corrected by using a determination of the colour produced from a known quantity of the *cis*-ether under the same conditions. It was assumed that all the reaction not leading initially to acraldehyde diethylacetal is equally partitioned between *cis*- and *trans*-chloro-3-ethoxyprop-1-ene; any error arising from this assumption will have a negligible effect on the calculated rate coefficients, since the correction itself is small.

† Measured after appropriate dilution.

These rate coefficients refer to the total reaction, as in the analogous case discussed by Cooper, Hughes, and Ingold (*J.*, 1937, 1280). Values determined at 85·4° (mean $10^4k_2 = 83·5$) enable one to calculate the activation energy as *ca.* 27 kcal. The dependence of second-order rate coefficients on concentration of sodium ethoxide is shown by the following relative values at 85·4°: 0·52N-NaOH, 1·0; 0·19N-NaOH, 1·1; 0·06N-NaOEt, 1·2. The rate of reaction is therefore dependent directly on the concentration of sodium ethoxide, with the usual slight modification due to a negative salt effect.



The percentages of acraldehyde diethyl acetal produced in the above reactions were 51·6% at 64·9° and 42·5% at 85·4°. These results indicate that the proportion of reaction proceeding by the S_N2 route to give acraldehyde diethyl acetal decreases with increased temperature.

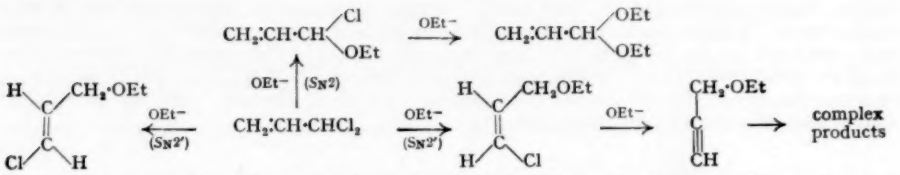
(ii) *Rate of development of chloride ion.* The composite bimolecular reaction of ethoxide ions with 3 : 3-dichloroprop-1-ene to yield derivatives of acraldehyde, as well as the 1-chloro-3-ethoxyprop-1-enes, releases between 100% and 50% of the theoretical amount of chlorine from the organic dichloride, depending on the ratio in which the component reactions contribute. To calculate a true rate constant for the production of chloride ion, it would be necessary to know the amount of chloride released when this reaction is completed. Unfortunately, the *cis*-chloro-ether, which is one of the products of the S_N2' reaction, undergoes, in the presence of ethoxide ion, elimination of hydrogen chloride at a rate similar to that of its formation from 3 : 3-dichloroprop-1-ene. Hence, determinations of chloride cannot easily be used to estimate the " infinity " value which is required for the calculation of true rate constants. For this reason, details are given of the rate of production of chloride ion only to show the existence of *trans*-1-chloro-3-ethoxyprop-1-ene in the final stages of the reaction. The figure shows the rate of development of chloride ion from 0·0294M-3 :3-dichloroprop-1-ene and 0·519N-sodium ethoxide at 124·9°. After approx. 4 hours, the initially rapid production of chloride had ceased, and the subsequent rate corresponded to a second-order coefficient of 0·00020. This agrees well both with the value obtained for the authentic *trans*-1-chloro-3-ethoxyprop-1-ene (0·000173 at 120°) and with that obtained for the ether isolated from the reaction product (0·000177 at 120°). The initial rapid production of chloride ion ceases at 88·3% release of chlorine, which corresponds with the production from 3 : 3-dichloroprop-1-ene of 23·4% of *trans*-ether.

(iii) *Rate of solvolysis.* Solvolysis of 3 : 3-dichloroprop-1-ene is too slow to allow the reaction to be followed conveniently for more than the initial part of the reaction; *e.g.*, after reaction for 1000 minutes at 85·6°, 2·28% of chlorine is released from the compound, and 0·62% of

acraldehyde diethyl acetal is produced. In the presence of 0·5N-sodium ethoxide under the same conditions, *ca.* 84% of chlorine and *ca.* 40% of acraldehyde diethyl acetal would have been produced. The solvolysis is thus a negligible factor in determining the kinetics of, and the products from, the reaction in the presence of sodium ethoxide, which is therefore a bimolecular process.

Discussion

(i) *Products of the Reaction.*—In view of the above experimental findings, the following scheme may be written for the reaction of 3 : 3-dichloroprop-1-ene with sodium ethoxide in ethyl alcohol :



Our most important task was to confirm that 1-chloro-3-ethoxyprop-1-ene forms a part of the product of the reaction. Conclusive evidence has now been given for the formation both of the *cis*- and of the *trans*-isomer of this substance. The *trans*-isomer, being the more stable to alkali, is the more easily isolated. The *cis*-isomer was identified only as a product of partial reaction, mixed with its *trans*-isomer, but reacted at a characteristic rate with alcoholic sodium ethoxide at 85·6°.

The weight of *trans*-ether isolated, in the experiment in which 11 g. of the dichloride should have undergone reaction, was 2·3 g., representing about 20% of the total reaction. One might presume that an equal quantity had been lost in intermediate fractions, and by decomposition of the *cis*-ether. The remainder of the reaction results in the production of acraldehyde diethyl acetal, which was isolated almost pure by careful fractionation of the product obtained when the reaction was forced to completion. The emphasis laid in earlier literature (cf. Huntress, *op. cit.*) on rearrangements accompanying bimolecular reactions of this dichloride is thus unjustified : both normal and rearranged products are important components of the reaction product; we shall also document them for the corresponding unimolecular processes.

(ii) *Mechanisms involved in the Reaction.*—The solvolysis of 3 : 3-dichloroprop-1-ene has been shown to be negligibly slow, compared with its reaction with ethoxide ions. The latter process, which results in the formation of acraldehyde diethyl acetal and the 1-chloro-3-ethoxyprop-1-enes, must therefore be almost exclusively of the second order.* Acraldehyde diethyl acetal is clearly the result of normal bimolecular substitution (S_N2), proceeding at the slow rate expected for a *gem*-dichloride, followed by rapid liberation of the second chlorine atom. The 1-chloro-3-ethoxyprop-1-enes form, however, a substantial part (40—50%) of the product. In view of the dependence of the rate of reaction on the concentration of alkali, these products of rearrangement must also be produced in a second-order process, which we consider to be a bimolecular substitution with anionotropic rearrangement (S_N2'). This conclusion is further strengthened by the kinetically simpler results for the corresponding reaction with sodium thiophenoxide described in the following paper.†

* This is shown also by the fact that, salt effects being neglected, the second-order rate-coefficients for the total reaction (measured by following the production of acraldehyde diethyl acetal as described above) do not vary with the concentration of sodium ethoxide.

† It might be supposed that the initial bimolecular process involved the removal of a proton : $CH_2{:}CH{\cdot}CHCl_2 + OEt^- \longrightarrow CH_2{:}CH{\cdot}CCl_2^-$. In the resulting carbanion, the charge would be distributed by mesomerism : $CH_2{:}CH{\cdot}CCl_2^- \longleftrightarrow {}^-CH_2{\cdot}CH{:}CCl_2$. There seems to be no reason why the presence of this charge should in any way facilitate the attachment of an ethoxy-group in the 3-position; indeed, it must retard any further approach by a nucleophilic reagent, while encouraging attachment of a proton to form the prototropically rearranged isomer, $CH_3{\cdot}CH{:}CCl_2$ which is very stable to alkali, particularly at low temperatures (cf. Smith and King, *loc. cit.*). We have not been able to isolate this compound from the reaction product, though we consider that a small amount (> 10%) may possibly be produced in the reaction.

Considering, in a general way, substitutions under bimolecular conditions of the type: $CH_2{:}CH{\cdot}CHR{\cdot}X + Y^-$, it has already been observed, as by England and Hughes (*loc. cit.*), that, for the commoner allyl structures (*e.g.*, R = Me), when these are attacked by the usual nucleophilic reagents (*e.g.*, Y = OH^-, Br^-, Cl^-, OEt^-), the direct (S_N2) substitution, compared with rearrangement (S_N2'), is favoured by a factor of the order of 10^2. Various possible methods exist for rendering the latter process experimentally accessible, including the following: (*a*) For the symmetrical case (Y = X), the S_N2 reaction regenerates the starting material, and the S_N2' reaction may be studied directly, as by England and Hughes (*loc. cit.*; R = Me, X = Y = Br). (*b*) R may be altered in such a way as to favour the S_N2' mechanism; and if at the same time the S_N2 process is hindered, the former mechanism may become predominant, as in the reaction studied in this investigation (R = Cl, Y = OEt); we are extending use of this principle to the investigation of related systems. (*c*) R may be altered in such a way as to inhibit sterically the S_N2 reaction, so that the S_N2' process becomes predominant, independently of its polar requirements. Such a case is at present under investigation in these laboratories by Mr. P. C. Merriman (R = Bu^t). (*d*) The relative reactivities of the reagent Y for the two positions may be altered in such a way as to favour the S_N2' mechanism. Kepner, Winstein, and Young (*J. Amer. Chem. Soc.*, 1949, **71**, 115) gave a possible example of this behaviour [R = Et, Y = $CH(CO_2Et)_2^-$], though doubt has been cast (*e.g.*, by Dewar, *Bull. Soc. chim.*, 1951, **18**, C 42) on the interpretation of the latter reaction as following the S_N2' mechanism.

Analyses are by Drs. Weiler and Strauss, of Oxford, and Mr. A. V. Winter of this Department. We thank Mr. E. Grayson for technical assistance. This work has developed as part of an investigation of mechanisms of anionotropic rearrangements initiated by Professors E. D. Hughes, F.R.S., and C. K. Ingold, F.R.S., to whom we are indebted for help and encouragement.

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641. *The Kinetics and Mechanisms of Nucleophilic Displacements in Allylic Systems. Part II.* The Reactions between 3 : 3-Dichloroprop-1-ene and the Thiophenoxide Ion.*

By P. B. D. DE LA MARE and C. A. VERNON.

3 : 3-Dichloroprop-1-ene reacts with sodium thiophenoxide by a reaction which has the kinetic form $-d[RCl_2]/dt = k[RCl_2][SPh^-]$, releases 81% of chlorine from the dichloride, and produces (together with a diphenylthiopropene), a mixture of *cis*- and *trans*-1-chloro-3-phenylthioprop-1-ene in *ca.* 38% yield. It is considered that these latter substances are formed by a bimolecular nucleophilic substitution with rearrangement (S_N2').

In Part I * it was shown that 3 : 3-dichloroprop-1-ene reacts with ethoxide ions by a bimolecular mechanism to form, together with products of normal substitution (S_N2), those involving anionotropic rearrangement (S_N2'). The reaction was, however, composite, and one of the products (*cis*-1-chloro-3-ethoxyprop-1-ene) rather rapidly underwent further elimination of hydrogen chloride under the conditions of the rate measurements. Furthermore, it was suspected, though not proved, that a small amount of prototropic rearrangement (forming 1 : 1-dichloroprop-1-ene and its products of decomposition) accompanied the main reaction.

It seemed desirable, therefore, to examine the reaction of 3 : 3-dichloroprop-1-ene with a reagent less likely to promote prototropic changes or elimination reactions. The thiophenoxide ion proved eminently suitable. This reagent has a small tendency to attach itself to a proton; *e.g.*, the acid dissociation constant of thiophenol has $pK = 9{\cdot}3$ in 95% ethanol (Schwartzenbach and Rudin, *Helv. Chim. Acta*, 1939, **22**, 1360), compared

* Part I, preceding paper.

with that of phenol, $pK = 12{\cdot}8$ in 95% ethanol (*idem, ibid.*) or of ethyl alcohol, $pK_{auto} = 19{\cdot}0$ (cf. Remick, "Electronic Interpretation of Organic Chemistry," Wiley and Sons, N.Y., p. 324). On the other hand, its reactivity towards a carbon centre is much more facile than that of either the ethoxide or the phenoxide ion. This high reactivity (cf. Quayle and Royal, *J. Amer. Chem. Soc.*, 1942, **64**, 227) applies also to nucleophilic displacement by RS^- ions at aromatic centres (Hodgson and Handley, *J. Soc. Chem. Ind.*, 1927, **46**, 435T; cf. Bunnett and Zahler, *Chem. Reviews*, 1951, **49**, 273), indicating that the phenomenon is not a property specifically of a saturated carbon atom. With these facts in mind, the kinetics and products of the reaction between 3 : 3-dichloroprop-1-ene and the thiophenoxide ion have been examined.

Experimental

Solutions of sodium thiophenoxide were prepared by adding the theoretical quantity of redistilled thiophenol (L. Light and Co.) to a solution of sodium ethoxide in ethyl alcohol. Conventional methods were used in following the rate of disappearance of this ion; aliquots of the reaction mixture were added to excess of standard acid, and back-titrated with standard alkali, bromophenol-blue being used as indicator. Other materials were as described in Part I (*loc. cit.*).

The following are details of a typical rate-measurement. Thiophenol (2·66 g.) was added to 255 ml. of 0·0953N-sodium ethoxide in ethyl alcohol, and 3 : 3-dichloroprop-1-ene (1·139 g.) was made up to 250 ml. with this solution. Aliquots of 5·53 ml. were added to 10 ml. of 0·1730N-hydrochloric acid, and back-titrated with 0·02025N-sodium hydroxide. The initial sample was taken after it had been allowed to warm to the temperature of the thermostat (24·7°) for ten minutes:

Time (min.)	0	160	252	313	386	438	1382	1692	3155	∞
Titre (ml. NaOH)	17·46	19·06	19·82	20·31	20·90	21·32	26·10	27·28	30·69	35·46
10^3k_2	—	6·53	6·35	6·34	6·42	6·51	6·43	6·62	7·00	—

Further tubes from the same batch being used, the following mean velocity coefficients were obtained: at 45·2°, $10^3k_2 = 64{\cdot}4$; at 65·3°, $10^3k_2 = 470$. From these values are derived the following Arrhenius parameters: $E = 21{\cdot}2$ kcal., $\log_{10} B$ * $= 13{\cdot}34$.

The runs were demonstrably of the second order, as is also shown by the results of varying the concentration of thiophenoxide ion at 45·2°; SPh^- = 0·0883, $10^3k_2 = 64{\cdot}4$; SPh^- = 0·2176, $10^3k_2 = 54{\cdot}2$. The small "dilution" (negative salt) effect characteristic of this class of second-order reactions in alcohol (cf. Hughes, Ingold, Masterman, and McNulty, *J.*, 1940, 903) is also manifest in these results.

The percentage of chlorine released from the dichloride in the above experiments was 81. Confirmation of this value was obtained by direct estimation of chloride at completion of the reaction, by potentiometric titration after organic substances had been removed by extraction from acid solution. Values obtained at different temperatures by this method were: 85°, 81%; 65°, 80%; 45°, 81%. These values reflect the proportions to which the S_N2 and the S_N2' reactions (releasing 2 and 1 equiv. of chlorine, respectively) contribute to the total process; it is clear that these processes have almost the same activation energy.

A single measurement was made of the rate of reaction of 3 : 3-dichloroprop-1-ene (0·069M) with sodium phenoxide (0·869M) in ethyl alcohol at 100°. Reaction had virtually ceased after the liberation of 89% of chlorine from the compound: the second-order rate coefficient for the whole process was 0·030 l. g.-mol.$^{-1}$ min.$^{-1}$.

Products of Reaction.—For reference *trans*-1-chloro-3-phenylthioprop-1-ene was prepared from *trans*-1 : 3-dichloropropene (1·5 g.), which was dissolved in a solution containing 15 ml. of thiophenol in 150 ml. of N-sodium ethoxide in ethyl alcohol. The reaction mixture was left overnight, and was then diluted with water and extracted three times with pentane. The extract was washed with water, dried, and evaporated to small bulk. On cooling to −80°, white crystals separated, which were recrystallised from pentane, and distilled *in vacuo* giving a product, b. p. 260°/770 mm. (decomp.), n_D^{25} 1·5900, m. p. 5° (Found: C, 58·8; H, 5·5; S, 17·0; Cl, 18·9. C_9H_9SCl requires C, 58·5; H, 4·9; S, 17·35; Cl, 19·25%). From *cis*-1 : 3-dichloro-

* Values of k_2 and B, units l. g.-mol.$^{-1}$ min.$^{-1}$, are calculated from the formulæ $k_2 = Be^{-E/RT} = [2{\cdot}303/t(a - x_\infty)] \log_{10} x_\infty(a - x_t)/a(x_\infty - x_t)$ where a is the initial concentration of SPh^- and x_t is the concentration of HCl produced by the reaction at time t; this is appropriate for calculation of second-order rate-coefficients for the total reaction.

propene there was obtained similarly cis-1-*chloro*-3-*phenylthioprop*-1-*ene* as an oil, b. p. 260°/770 mm. (decomp.), n_D^{25} 1·5891 (Found: C, 57·9; H, 4·7%).

When 27 g. of 3 : 3-dichloroprop-1-ene were mixed with 800 ml. of 0·63N-sodium thiophenoxide, the solution became warm, and sodium chloride was precipitated. The reaction was completed at 60°, and the product was poured into water and extracted with pentane. The washed and dried extract was fractionated at reduced pressure; a middle fraction, 6·6 g., had b. p. 76°/*ca.* 0·5 mm., n_D^{25} 1·5888 (Found: C, 58·8; H, 5·0; S, 16·9; Cl, 19·2%), of the same m. p. (−11°) as an equimolar mixture of *cis*- and *trans*-1-chloro-3-phenylthioprop-1-ene. After two recrystallisations from pentane at low temperature, there were obtained 2 g. of material, n_D^{25} 1·5901 (Found: C, 59·1; H, 5·1; S, 17·0; Cl, 18·9%), m. p. 5° unchanged on admixture with an authentic specimen of *trans*-1-chloro-3-phenylthioprop-1-ene.

The higher-boiling material was statically distilled at *ca.* 0·03 mm., giving 27 g. of material, n_D^{25} 1·6456, and leaving a residue of tar. A middle fraction, n_D^{25} 1·6479, from this material gave the following analysis: C, 68·5; H, 5·7; S, 25·2 ($C_{15}H_{14}S_2$ requires C, 69·8; H, 5·4; S, 24·8%) and hence, by analogy with the formation of $CH_2{:}CH{\cdot}CH(OEt)_2$ from 3 : 3-dichloroprop-1-ene and ethoxide ions (Part I) is 3 : 3(?)-*diphenylthioprop*-1-*ene*, $CH_2{:}CH{\cdot}CH(SPh)_2$, a final product of the S_N2 displacement of chlorine. This formulation is also consistent with the ultra-violet absorption spectrum of the compound, which was determined by Dr. D. P. Craig, using a Carey recording spectrophotometer. In alcoholic solution, there was a maximum molecular extinction coefficient ($\varepsilon_{max.}$) of 13,800 at 2515 Å, with a shoulder on the absorption curve at about 2600 Å. The compound $CH_2{\cdot}CH(SPh)_2$ has $\varepsilon_{max.}$ = 10,000 at 2560 Å (Fehnel and Carmack, *J. Amer. Chem. Soc.*, 1949, **71**, 2889), and the absorption curves of the two compounds have very similar shapes.

Discussion

The reaction of 3 : 3-dichloroprop-1-ene with the thiophenoxide ion follows the kinetic law $-d[RCl_2]/dt = k[RCl_2][SPh^-]$. It is therefore a bimolecular displacement, a large component of which leads to the formation of the rearranged thio-ether $SPh{\cdot}CH_2{\cdot}CH{:}CHCl$. This is to be interpreted, in our opinion, as the result of a bimolecular nucleophilic displacement with anionotropic rearrangement, S_N2'. The present example is kinetically less complex than the corresponding reaction involving ethoxide ions (Part I, *loc. cit.*), since the initial products are stable in the presence of the reagent. It is possible to determine with reasonable accuracy the Arrhenius parameters of the individual processes, which both have an activation energy of 21·2 kcal.; the values of $\log_{10} B$ are, for the S_N2 and S_N2' reactions respectively, 13·20 and 12·92. Thus the non-exponential term in the Arrhenius equation for the reaction which leads to rearrangement shows no particular abnormality, being within the range of values typical of reactions between negative ions and neutral molecules, in accordance with the similar results of England and Hughes (*Nature*, 1951, **168**, 1002).

The following figures illustrate the relative contribution of the S_N2 and S_N2' processes to the reaction of 3 : 3-dichloroprop-1-ene with various reagents:

Reagent	OEt^-	OPh^-	SPh^-
Total rate of substitution, k_2 (l. g.-mol.$^{-1}$ min.$^{-1}$)	0·036	0·030	8·73
% Cl released	*ca.* 70	89	81
% S_N2'	*ca.* 40	22	38

The data are not extensive enough to allow generalisation, but it seems that the relative ease of attack by the nucleophilic reagent at the two positions is not very critically dependent on the nature of the anion.* Consequently, this compound, in such reactions, is likely usually to give a mixture containing a substantial quantity of both normal and rearranged product. It is to be noted that, as far as can be deduced from the present experiments, *cis*- and *trans*-olefinic compounds are produced in approximately equal amount by the S_N2' reaction.

The above comparison of the total rate of substitution illustrates the exceptional

* It is not possible to be certain whether the comparable solvolysis of this compound with ethyl alcohol is uni- or bi-molecular: but the results given in Part I make it clear that the use of a neutral molecule replacing an anion as the nucleophilic reagent does not to any great degree, if at all, favour the rearrangement, since a good proportion of acraldehyde diethylacetal is also produced in the solvolysis.

nucleophilic power of the thiophenoxide ion towards a carbon centre. The nucleophilic power of anions is often associated with their affinities for a proton, but comparison indicates the limitations of this correlation (cf. also Hughes, *Quart. Reviews*, 1951, **5**, 245), since compounds of the type RSH are much stronger acids than the corresponding compounds of the type ROH.

We are indebted to Dr. D. P. Craig for the ultra-violet absorption measurements, and to Professor E. D. Hughes for his continued encouragement. Analyses are due to Drs. Weiler and Strauss, of Oxford, and to Mr. A. V. Winter, of this Department. We thank Mr. E. Grayson for technical assistance.

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642. *Aminoalkanesulphonamides and Alkanedisulphonamides.*

By J. W. Griffin and D. H. Hey.

A general method has been developed for the preparation of ω-amino-alkane-α-sulphonamides $NH_2 \cdot [CH_2]_x \cdot SO_2 \cdot NH_2$ and of alkane-αω-disulphonamides $NH_2 \cdot SO_2 \cdot [CH_2]_y \cdot SO_2 \cdot NH_2$, which is illustrated by the examples in which x is 2, 3, 4, and 5, and y is 3, 4, 5, and 10. A number of the corresponding sulphonylacetamides and sulphonamidopyridines is also described.

The concept that compounds chemically related to a metabolite may interfere with its normal function in the living cell instigated the present investigation, begun in 1946, into the methods of preparation and properties of some sulphonamides of the aliphatic series. The special pharmacological properties associated with marfanil (*p*-aminomethylbenzenesulphonamide) and in particular its non-inhibition by *p*-aminobenzoic acid (Klarer, *Klin. Wschr.*, 1941, **20**, 1250; Domagk, *ibid.*, 1942, **21**, 448; Evans, Fuller, and Walker, *Lancet*, 1944, II, 523; Mitchell, Rees, and Robinson, *Lancet*, 1944, I, 627) suggested that certain advantages might be associated with the presence of the more basic aliphatic amino-group (cf. Havinga and Veldstra, *Rec. Trav. chim.*, 1947, **66**, 257). Further, the recognition of the importance of amino-acids in metabolic processes suggested that the properties of the structurally related amino-sulphonic acids (or their amides) deserved attention. Work on similar lines has already been reported by McIlwain (*J.*, 1941, 75), Mead, Rapport, Senear, Maynard, and Koepfli (*J. Biol. Chem.*, 1946, **163**, 467), Ravel and Shive (*ibid.*, 1946, **166**, 407), and others. The present investigation is restricted to the ω-aminoalkane-α-sulphonamides, which may be regarded as being related to β-alanine, γ-aminobutyric acid, δ-aminovaleric acid, and 6-aminohexanoic acid and their derivatives, and to some alkane-αω-disulphonamides. In the latter connection reference may be made to the relation between pimelic acid and biotin (cf. also Iványovics and Vargha, *Z. physiol. Chem.*, 1944, **281**, 156) and to the isolation, by Work, of αε-diaminopimelic acid as a new naturally occurring amino-acid (*Proc. Biochem. Soc.*, 1950, v).

Some aminoalkanesulphonamides have been reported by Christiansen (U.S.P. 2,184,279/1940), who claimed that they possessed antibacterial properties. Miller, Sprague, Kissinger, and McBurney (*J. Amer. Chem. Soc.*, 1940, **62**, 2099) have also prepared 2-aminoethane-, 3-aminopropane-, and 4-aminobutane-1-sulphonamide, but declared them to be inactive. Their biological tests were confined, however, to streptococcal infections in mice and because of this the specific activity of marfanil, the preparation of which was included in the same communication, was overlooked by these workers. The method used by Miller, Sprague, Kissinger, and McBurney (*loc. cit.*) for the preparation of the amino-sulphonamides $NH_2 \cdot [CH_2]_n \cdot SO_2 \cdot NH_2$, in which $n = 3$ and 4, consisted of the conversion of the appropriate chloro-nitrile (I) into the *S*-cyanoalkylthiuronium chloride (II), which was then converted by the action of chlorine in cold aqueous solution into the sulphonyl chloride (III) (cf. Johnson and Sprague, *J. Amer. Chem. Soc.*, 1936, **58**, 1348; 1937, **59**, 1837). The last

was treated with ammonia and then submitted to catalytic hydrogenation, to give the amino-sulphonamide (IV) :

$$\underset{(I)}{CN\cdot[CH_2]_n\cdot Cl} \longrightarrow \underset{(II)}{CN\cdot[CH_2]_n\cdot S\cdot C(:NH)\cdot NH_2,HCl} \longrightarrow \underset{(III)}{CN\cdot[CH_2]_n\cdot SO_2Cl} \longrightarrow$$

$$CN\cdot[CH_2]_n\cdot SO_2\cdot NH_2 \longrightarrow \underset{(IV)}{NH_2\cdot[CH_2]_{n+1}\cdot SO_2\cdot NH_2}$$

This method failed when $n = 1$ and for this member 2-chloroethylphthalimide (V; $n = 2$) was used in a similar sequence of reactions which may be represented as follows (X> = *o*-$C_6H_4\langle^{CO}_{CO}\rangle$; Py = 2-pyridyl) :

$$\underset{(V)}{X{>}N\cdot[CH_2]_n\cdot Cl} \longrightarrow \underset{(VI)}{X{>}N\cdot[CH_2]_n\cdot S\cdot C(:NH)\cdot NH_2,HCl} \longrightarrow \underset{(VII)}{X{>}N\cdot[CH_2]_n\cdot SO_2Cl}$$

$$\downarrow$$

$$\underset{(X)}{NHAc\cdot[CH_2]_n\cdot SO_2\cdot NHAc} \longleftarrow \underset{(IX)}{HCl,NH_2\cdot[CH_2]_n\cdot SO_2\cdot NH_2} \longleftarrow \underset{(VIII)}{X{>}N\cdot[CH_2]_n\cdot SO_2\cdot NH_2}$$

$$\downarrow$$

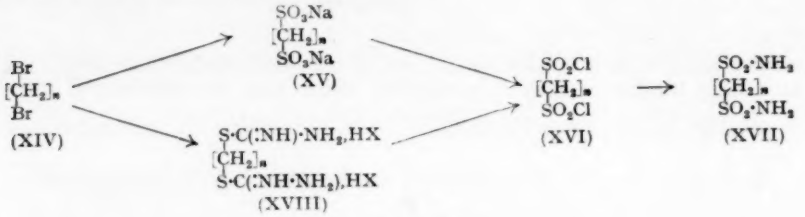
$$(VII) \longrightarrow \underset{(XII)}{X{>}N\cdot[CH_2]_n\cdot SO_2\cdot NHPy} \longrightarrow \underset{(XIII)}{H_2N\cdot[CH_2]_n\cdot SO_2\cdot NHPy} \qquad \underset{(XI)}{X{>}N\cdot[CH_2]_n\cdot SO_2\cdot NHAc}$$

Repetition of the former method, based on the chloro-nitrile, having given unsatisfactory results, attention was directed to the second route based on the halogenoalkylphthalimide, but in place of the chloro-compound the bromo-compound was used following numerous reports that bromides react more readily with thiourea than do the corresponding chlorides (Johnson and Sprague, *loc. cit.*; Urquhart, Gates, and Connor, *Org. Synth.*, 1941, **21**, 37; Frank and Smith, *J. Amer. Chem. Soc.*, 1946, **68**, 2103). This modification necessitated the conversion of the thiuronium bromides (as VI) into the acetates and then into the chlorides (VI) before the treatment with chlorine, but these stages presented no difficulty and the sulphonyl chlorides (VII) were obtained in good yields. The latter were converted into the sulphonamides in benzene solution by means of dry ammonia, which gave improved yields (cf. Miller *et al.*, *loc. cit.*). By this sequence of reactions the ω-aminoalkanesulphonamide hydrochlorides (IX) in which $n = 2$, 3, 4, and 5 were prepared. The method failed with both *N*-chloro- and *N*-bromo-methylphthalimide (as V; $n = 1$) at the chlorination stages (VI ⟶ VII). Miller *et al.* (*loc. cit.*) have also reported a failure with *S*-cyanomethylthiuronium chloride (II; $n = 1$).

2-Phthalimidoethane-1-sulphonamide (VIII; $n = 2$) and 3-phthalimidopropane-1-sulphonamide (VIII; $n = 3$) were converted into their acetyl derivatives (XI). The phthalimidoalkane-1-sulphonyl chlorides (VII; $n = 3$, 4, and 5) were condensed with 2-aminopyridine and the resulting 2-(phthalimidoalkanesulphonamido)pyridines (XII) were converted into (XIII; $n = 3$, 4, and 5), the last two bases being isolated as hydrochlorides. The corresponding compound in the ethane series has been reported by Mead *et al.* (*loc. cit.*) and by Winterbottom, Clapp, Miller, English, and Roblin (*J. Amer. Chem. Soc.*, 1947, **69**, 1393). The amino-sulphonamides $NH_2\cdot[CH_2]_n\cdot SO_2\cdot NH_2$, in which $n = 2$, 3, 4, and 5, were also converted into the corresponding acetamidoalkanesulphonylacetamides (X; $n = 2$, 3, 4, and 5).

A few alkane-αω-disulphonamides have been prepared by means of the reactions (XIV ⟶ XV ⟶ XVI ⟶ XVII) (Clutterbuck and Cohen, *J.*, 1922, **121**, 120; Autenrieth and Bölli, *Ber.*, 1925, **58**, 2149; Helferich and Grünert, *Ber.*, 1941, **74**, 1531). Johnson and Sprague (*loc. cit.*) have also prepared ethane-1 : 2-disulphonyl chloride (XVI; $n = 2$) by the action of chlorine on a cold aqueous solution of *SS*-ethylenebisthiuronium chloride (XVIII; $n = 2$, X = Cl). This method has now been applied to the alkylene-αω-bisthiuronium chlorides (XVIII; X = Cl) for the examples in which $n = 3$, 4, 5, and 10,

the chlorides being prepared from the bisthiuronium bromides through the acetates. In this manner the four αω-disulphonamides were conveniently obtained. Three of them were converted into their diacetyl derivatives and in addition pentane-1 : 5-disulphonamide was converted by the method of Birtwell, Haworth, Rose, Swain, and Vasey (*J.*, 1946, 491) into pentane-1 : 5-bis-sulphonylguanidine.



Experimental

2-Aminoethane-1-sulphonamide Hydrochloride.—2-Phthalimidoethanesulphonyl chloride was prepared from *N*-2-chloroethylphthalimide (Wenker, *J. Amer. Chem. Soc.*, 1937, **59**, 422) by the method of Miller *et al.* (*loc. cit.*) and converted into 2-phthalimidoethanesulphonamide, m. p. 209—210°. Removal of the phthaloyl group by means of hydrazine hydrate, as described by Miller *et al.*, gave 2-aminoethane-1-sulphonamide hydrochloride in needles, m. p. 131—133·5°, from 95% aqueous ethanol (Found : C, 15·0; H, 5·8. Calc. for $C_2H_8O_2N_2S,HCl$: C, 15·0; H, 5·6%). A solution of 2-aminoethane-1-sulphonamide hydrochloride (1·2 g.) in acetic anhydride (10 c.c.) was heated under reflux at 150—160° for 15 minutes. The excess of acetic anhydride was removed by boiling the mixture with alcohol in an open vessel. The solid residue was crystallised from alcohol. *2-Acetamidoethane-1-sulphonylacetamide* (0·52 g.) separated in colourless plates, m. p. 153·5—154·5° (Found : C, 34·0; H, 5·8; N, 13·8. $C_6H_{12}O_4N_2S$ requires C, 34·6; H, 5·8; N, 13·5%).

S-3-Phthalimidopropylthiuronium Bromide.—1 : 3-Dibromopropane, b. p. 166° (Kamm and Marvel, *Org. Synth.*, Coll. Vol. I., edn. 2, p. 30) was converted into *N*-3-bromopropylphthalimide, m. p. 72°, by the method of Ing and Manske (*J.*, 1926, 2348). A mixture of the latter (414·5 g.), thiourea (117 g.), and 95% aqueous alcohol (830 c.c.) was boiled under reflux for 8 hours. When cold the precipitated salt was collected, washed with cold alcohol, and dried (434 g.; m. p. 218°). Crystallisation from water gave *S-3-phthalimidopropylthiuronium bromide* in colourless hexagonal plates, m. p. 226—228° (decomp.) (Found : C, 42·3; H, 4·3; N, 11·2. $C_{12}H_{14}O_2N_3BrS$ requires C, 41·9; H, 4·1; N, 12·2%).

3-Phthalimidopropane-1-sulphonyl Chloride.—A hot saturated aqueous solution of potassium acetate (117 g. in 102 c.c.) was added with stirring to a hot aqueous solution of *S*-3-phthalimidopropylthiuronium bromide (105 g. in 800 c.c.). The temperature was kept at 80° and the crystalline *S*-3-phthalimidopropylthiuronium acetate began to separate almost at once. The mixture was cooled and the thiuronium acetate was collected and dried [86 g.; m. p. 152·5—153·5° (decomp.)]. Chlorine was passed at 0—5° into a suspension of the thiuronium acetate (86 g.) in water (680 c.c.) to which concentrated hydrochloric acid (9 g.) had been added. After 3 hours the 3-phthalimidopropane-1-sulphonyl chloride was filtered from the green solution and washed with cold water. The crude sulphonyl chloride was dried (69 g.) and extracted with the minimum quantity of hot dry benzene. Addition of light petroleum (b. p. 40—60°) to the cooled benzene solution precipitated *3-phthalimidopropane-1-sulphonyl chloride* (64 g.; m. p. 84—87°) (Found : C, 45·9; H, 3·7; Cl, 12·2. $C_{11}H_{10}O_4NClS$ requires C, 45·9; H, 3·5; Cl, 12·3%). The m. p., on recrystallisation from benzene–light petroleum (b. p. 40—60°), dropped to 76—78°, whereas crystallisation from hot benzene gave material of m. p. 82—85°, which when the substance was kept *in vacuo* over concentrated sulphuric acid again dropped to 76—78°.

3-Phthalimidopropane-1-sulphonamide.—Dry ammonia was passed into a solution of 3-phthalimidopropane-1-sulphonyl chloride (53 g.) in dry benzene kept at 40° by means of external cooling. After 1½ hours precipitation was complete and the solvent was evaporated. The residue was treated with a small quantity of cold water to remove ammonium chloride, and the residual *3-phthalimidopropane-1-sulphonamide* was collected. It separated from boiling water or aqueous alcohol in plates, m. p. 170·5—173° (Found : C, 49·3; H, 4·6; N, 11·0. $C_{11}H_{12}O_4N_2S$ requires C, 49·3; H, 4·5; N, 10·5%).

3-*Aminopropane*-1-*sulphonamide Hydrochloride*.—Aqueous hydrazine hydrate (5·9 g. of 30% solution) was added dropwise with stirring to a suspension of 3-phthalimidopropane-1-sulphonamide (14·6 g.) in boiling alcohol (250 c.c.) under reflux. After 3 hours the mixture was cooled and filtered and the filtrate was evaporated to dryness under reduced pressure. A solution of the residue in water (600 c.c.) at 70° was acidified to Congo-red with hydrochloric acid. When cold the precipitated phthalhydrazide was removed and the filtrate evaporated to dryness. Water (10 c.c.) was added to the residue, and the solution was filtered. Evaporation gave the crude 3-aminopropanesulphonamide hydrochloride (8 g.), which after purification by crystallisation from 80% aqueous alcohol was obtained in colourless prisms, m. p. 161—163° (Found: C, 21·5; H, 6·2; N, 16·1. Calc. for $C_3H_{10}O_2N_2S,HCl$: C, 20·6; H, 6·3; N, 16·0%). Miller *et al.* (*loc. cit.*) recorded m. p. 159—160° for this hydrochloride prepared by the catalytic reduction of 2-cyanoethane-1-sulphonamide. Acetic anhydride (0·3 g.) was added to a solution of 3-aminopropane-1-sulphonamide hydrochloride (0·5 g.) in aqueous sodium hydroxide (0·23 g. in 25 c.c.). After five minutes' shaking alcohol was added and the solution evaporated to dryness. From the residue hot acetone extracted **3-*acetamidopropane*-1-*sulphonamide*** (0·3 g.), which separated from alcohol in colourless plates, m. p. 121·5—123° (Found: C, 34·0; H, 6·7; N, 15·3. $C_5H_{12}O_3N_2S$ requires C, 33·6; H, 6·7; N, 15·6%).

3-*Acetamidopropane*-1-*sulphonylacetamide*, prepared as described above for the corresponding derivative of ethane, separated from alcohol in plates, m. p. 162·5—163·5° (Found: C, 38·1; H, 6·5; N, 12·2. $C_7H_{14}O_4N_2S$ requires C, 37·8; H, 6·3; N, 12·6%).

S-4-*Phthalimidobutylthiuronium Bromide*.—A mixture of 1 : 4-dibromobutane (860 g.; Fried and Kleene, *J. Amer. Chem. Soc.*, 1940, **62**, 3258), finely powdered anhydrous potassium carbonate (121 g.), and phthalimide (245 g.) was heated under reflux at 180—190° for 2 hours. The product was separated into 1 : 4-diphthalimidobutane (28 g.; m. p. 224—226°, from acetic acid) and *N*-4-bromobutylphthalimide (280 g.; m. p. 79—80·5°) as in the preparation of the corresponding derivatives of propane. 1 : 4-Dibromobutane (507 g.) was recovered. From *N*-4-bromobutylphthalimide (280 g.) and thiourea (78·8 g.) in 95% aqueous alcohol (650 c.c.), after 22 hours' boiling, **S-4-*phthalimidobutylthiuronium bromide*** (329·5 g.) was obtained in plates, m. p. 174·5—177° (from boiling water) (Found: C, 11·4. $C_{13}H_{16}O_2N_3BrS$ requires N, 11·7%).

4-*Aminobutane*-1-*sulphonamide Hydrochloride*.—By the methods described above for the corresponding derivatives of propane, *S*-4-phthalimidobutylthiuronium bromide (104 g.) gave **4-*phthalimidobutane*-1-*sulphonyl chloride*** (60 g.) in plates, m. p. 126·5—128° (from acetone) (Found: Cl, 12·0; N, 4·4. $C_{12}H_{12}O_4NClS$ requires Cl, 11·8; N, 4·6%). This sulphonyl chloride (40 g.) gave a mixture of ammonium chloride and the amide, which was extracted with hot acetone. Evaporation of the solvent gave **4-*phthalimidobutane*-1-*sulphonamide*** (21·8 g.), which separated from alcohol in plates, m. p. 148·5—149·5° (Found: C, 51·0; H, 4·8; N, 9·6. $C_{12}H_{14}O_4N_2S$ requires C, 51·1; H, 5·0; N, 9·9%). The amide (21·8 g.) was converted into 4-aminobutane-1-sulphonamide hydrochloride (5·7 g.), m. p. 129—129·5° (after crystallisation from 90% alcohol) (Found: C, 26·0; H, 6·8; N, 14·6. Calc. for $C_4H_{13}O_2N_2S,HCl$: C, 25·5; H, 6·9; N, 14·9%). Miller *et al.* (*loc. cit.*) have recorded m. p. 127—129° for this hydrochloride prepared by the catalytic reduction of 3-cyanopropane-1-sulphonamide. **4-*Acetamidobutane*-1-*sulphonylacetamide***, prepared as described for the corresponding derivative of ethane, separated from alcohol in plates, m. p. 143—144·5° (Found: C, 41·1; H, 6·6; N, 11·8. $C_8H_{16}O_4N_2S$ requires C, 40·7; H, 6·8; N, 11·9%).

S-5-*Phthalimidoamylthiuronium Bromide*.—A mixture of 1 : 5-dibromopentane (470 g.; prepared in 80% yield from pentane-1 : 5-diol by the general procedure of Kamm and Marvel, *loc. cit.*), anhydrous potassium carbonate (62 g.), and phthalimide (130 g.) was heated under reflux at 190—200° for 4 hours. The excess of 1 : 5-dibromopentane (270 g.) was removed by distillation with steam. When cold the reaction flask contained two layers. The lower layer was separated by addition of chloroform, washed with water, and dried ($CaCl_2$). The syrup obtained on removal of the chloroform was triturated with light petroleum (b. p. 40—60°) and a little absolute alcohol. Extraction with light petroleum (b. p. 80—100°) of the solid thus obtained (171 g.) left a residue of 1 : 5-phthalimidopentane (11·2 g.), m. p. 182—183°, while removal of the solvent under reduced pressure gave *N*-5-bromoamylphthalimide (145 g.), m. p. 59—62°. The latter, with thiourea (39 g.) in 95% aqueous alcohol, was heated under reflux for 17 hours and gave **S-5-*phthalimidoamylthiuronium bromide*** (151 g.), isolated as in the previous examples, in needles, m. p. 188·5—189·5°, from ethyl alcohol (Found: C, 45·4; H, 5·0; N, 11·1. $C_{14}H_{18}O_2N_3BrS$ requires C, 45·2; H, 4·8; N, 11·3%).

5-*Aminopentane*-1-*sulphonamide Hydrochloride*.—By the methods described above, *S*-5-phthalimidoamylthiuronium bromide (42 g.) gave **5-*phthalimidopentane*-1-*sulphonyl chloride***

(34 g.) in needles, m. p. 77—79°, from benzene–light petroleum (b. p. 60—80°) (Found: C, 49·2; H, 4·4; N, 4·2; Cl, 11·7. $C_{13}H_{14}O_4NClS$ requires C, 49·4; H, 4·4; N, 4·4; Cl, 11·3%). This (5·5 g.) gave *5-phthalimidopentane-1-sulphonamide* (3·5 g.) in needles, m. p. 163·5—164·5°, from boiling water (Found: C, 52·8; H, 5·4; N, 8·9. $C_{13}H_{16}O_4N_2S$ requires C, 52·7; H, 5·4; N, 9·5%). The amide (4·5 g.) gave *5-aminopentane-1-sulphonamide hydrochloride* (2 g.), which separated from alcohol in fine hygroscopic needles, m. p. 126·5—129° (Found: C, 29·9; H, 7·9; N, 14·0. $C_5H_{14}O_2N_2S,HCl$ requires C, 29·6; H, 7·4; N, 13·8%). *5-Acetamidopentane-1-sulphonylacetamide*, prepared as described for the corresponding derivative of ethane, separated from alcohol in rhombohedra, m. p. 114—115° (Found: C, 43·5; H, 7·3; N, 11·2. $C_9H_{18}O_4N_2S$ requires C, 43·2; H, 7·2; N, 11·2%).

S-*Phthalimidomethylthiuronium Bromide*.—Thiourea (1·8 g.) and *N*-bromomethylphthalimide (5 g.; Pucher and Johnson, *J. Amer. Chem. Soc.*, 1922, **44**, 820) in dry benzene (25 c.c.) were boiled under reflux for 24 hours. When cold the mixture was filtered and the residue was washed with hot benzene to remove unchanged *N*-bromomethylphthalimide (1·4 g.). Crystallisation from aqueous alcohol gave S-*phthalimidomethylthiuronium bromide* (3·15 g.) in prisms, m. p. 219—220° (decomp.) (Found: C, 39·1; H, 3·3; N, 13·1. $C_{10}H_{10}O_2N_2BrS$ requires C, 40·0; H, 3·2; N, 13·3%).

S-*Phthalimidomethylthiuronium Chloride*.—In similar manner, thiourea (5·4 g.) and *N*-chloromethylphthalimide (13·7 g.; Sachs, *Ber.*, 1898, **31**, 1232), after being boiled in alcohol (50 c.c.) for 60 hours, gave S-*phthalimidomethylthiuronium chloride* (17 g.), which separated from alcohol in needles, m. p. 216° (Found: C, 43·8; H, 3·9; N, 15·4. $C_{10}H_{10}O_2N_2ClS$ requires C, 44·2; H, 3·7; N, 15·5%).

Action of Chlorine on S-*Phthalimidomethylthiuronium Salts in Aqueous Solution*.—The action of chlorine at 0—5° on an aqueous suspension of the acetate, prepared in the usual manner from the bromide, gave only a small quantity of a greyish gum. Similar treatment of the thiuronium bromide (9 g.) gave only *N*-chloromethylphthalimide (1·7 g.), m. p. 133·5—135°; in an experiment with the thiuronium chloride (2 g.) only *N*-hydroxymethylphthalimide (0·6), m. p. 145—148°, was isolated (Found: C, 60·5; H, 3·9. Calc. for $C_9H_7O_3N$: C, 61·0; H, 4·0%).

2-Phthalimidoethane-1-sulphonylacetamide.—A solution of 2-phthalimidoethanesulphonamide (1 g.) in acetic anhydride (10 c.c.) containing one drop of concentrated sulphuric acid was boiled under reflux for 15 minutes. The *acetyl* derivative (0·8 g.), which separated when the solution was poured into water, crystallised from 50% ethyl alcohol in needles, m. p. 194—195° (Found: C, 48·3; H, 4·2; N, 8·9. $C_{12}H_{12}O_5N_2S$ requires C, 48·7; H, 4·1; N, 9·5%). In similar manner there was prepared *3-phthalimidopropane-1-sulphonylacetamide* in prisms (from alcohol), m. p. 175—176° (Found: C, 50·5; H, 4·4; N, 9·0. $C_{13}H_{14}O_5N_2S$ requires C, 50·3; H, 4·5; N, 9·0%).

2-3′-Phthalimidopropanesulphonamidopyridine.—Finely powdered 3-phthalimidopropane-1-sulphonyl chloride (33 g.) was added during 15 minutes to a solution of 2-aminopyridine (22 g.) in dry benzene (340 c.c.). The solution was stirred and kept at room temperature (cooling) for 2 hours. The precipitate was collected, washed successively with a little benzene, cold alcohol, 1% aqueous sodium hydrogen carbonate, and water, and then dried *in vacuo*. The crude product (24·5 g.) separated from glacial acetic acid in prisms and from benzene in needles, m. p. 169·5—170·5° (Found: C, 55·7; H, 4·4; N, 12·2. $C_{16}H_{15}O_4N_3S$ requires C, 54·7; H, 4·5; N, 11·8%).

2-3′-Aminopropanesulphonamidopyridine.—By the procedure for the removal of the phthalimido-group outlined above 2-3′-phthalimidopropanesulphonamidopyridine (20·7 g.) gave the hydrochloride (18·5 g.), which was dissolved in a little water to which sodium hydrogen carbonate was then added. Evaporation left a syrupy residue which was extracted with 50% alcohol and boiled with charcoal. On concentration and cooling, *2-3′-aminopropanesulphonamidopyridine* (1·4 g.) separated in yellowish plates, m. p. 182·5—183·5° (Found: C, 44·6; H, 5·8; N, 18·9. $C_8H_{13}O_2N_3S$ requires C, 44·7; H, 6·1; N, 19·5%). It was almost insoluble in hot alcohol, but very soluble in cold water.

2-4′-Aminobutanesulphonamidopyridine Hydrochloride.—In similar manner 4-phthalimidobutane-1-sulphonyl chloride (60 g.) and 2-aminopyridine (37·5 g.) after 4 hours gave *2-4′-phthalimidobutanesulphonamidopyridine*, which separated as a viscous semi-solid which became granular after washing (28·3 g.). Crystallisation from glacial acetic acid gave needles (18·7 g.), m. p. 191·5—193·5° (Found: C, 56·0; H, 5·0; N, 11·6. $C_{17}H_{17}O_4N_3S$ requires C, 56·8; H, 4·7; N, 11·7%). The phthalimido-derivative (14·7 g.) on treatment with 30% hydrazine hydrate solution (4·4 g.) in hot alcohol (200 c.c.) gave the crude hydrochloride, which was extracted (Soxhlet) with hot alcohol. *2-4′-Aminobutanesulphonamidopyridine hydrochloride* (5·5 g.)

separated from the extract in colourless plates, m. p. 136·5—137·5° (Found: N, 15·2. $C_9H_{18}O_2N_2S$,HCl requires N, 15·8%).

2-5′-*Phthalimidopentanesulphonamidopyridine*.—(*a*) By the procedure described above, 5-phthalimidopentane-1-sulphonyl chloride (34 g.) and 2-aminopyridine (21 g.) in dry benzene (340 c.c.) gave 2-5′-*phthalimidopentanesulphonamidopyridine* (16·6 g.), which separated from hot methyl alcohol in cream-coloured prisms, m. p. 144·5—145·5° (Found: C, 57·9; H, 5·2; N, 10·7. $C_{18}H_{19}O_4N_3S$ requires C, 57·9; H, 5·1; N, 11·3%). (*b*) (cf. Winterbottom *et al.*, *loc. cit.*). The phthalimido-sulphonyl chloride (2 g.) was added in portions to a stirred solution of 2-aminopyridine (1·2 g.) in dry pyridine (5 c.c.) at 0°. The red reaction mixture was allowed to warm to room temperature and poured into an excess of 1·5N-hydrochloric acid with stirring. The solid which separated was collected, washed with cold water, and recrystallised from methyl alcohol. 2-5′-Phthalimidopentanesulphonamidopyridine (0·32 g.) was obtained in prisms, m. p. 145—147° undepressed on admixture with a specimen prepared by method (*a*) above.

2-5′-*Aminopentanesulphonamidopyridine Hydrochloride*.—2-5′-Phthalimidopentanesulphonamidopyridine (15·8 g.), suspended in hot alcohol (150 c.c.), on treatment with 35% hydrazine hydrate (4·2 g.), as described in the previous examples, gave 2-5′-*aminopentanesulphonamidopyridine hydrochloride* (7 g.) which separated from alcohol in colourless plates, m. p. 127·5—129° (Found: C, 43·4; H, 6·3; N, 14·3; Cl, 13·2. $C_{10}H_{17}O_2N_3S$,HCl requires C, 42·9; H, 6·4; N, 15·0; Cl, 12·7%).

Propylene-1 : 3-*bisthiuronium Bromide*.—A mixture of 1 : 3-dibromopropane (101 g.) and thiourea (76 g.) in 95% alcohol (375 c.c.) was boiled under reflux for 18 hours. When cold a syrup separated which became crystalline on trituration. The *thiuronium bromide* (153 g.) separated from aqueous alcohol in needles, m. p. 196·5—199·5° (Found: C, 18·0; H, 4·0; N, 16·0. $C_5H_{14}N_4Br_2S_2$ requires C, 17·0; H, 4·0; N, 15·8%).

Propane-1 : 3-*disulphonamide*.—A cold solution of potassium acetate (11·1 g.) in water (4·6 c.c.) was added to a cold solution of propylene-1 : 3-bisthiuronium bromide (20 g.) in water (20 c.c.) at <20°. The precipitated dithiuronium acetate was collected (m. p. 125—127°) and to its solution in water (160 c.c.) was added concentrated hydrochloric acid (13 g.). Chlorine was passed into the solution at 0—10°. The solid which separated melted on warming to room temperature and was extracted with chloroform. The extract was washed with aqueous sodium hydrogen sulphite and with water, and dried ($MgSO_4$). Removal of the solvent under reduced pressure left the propane-1 : 3-disulphonyl chloride as an oil (5·4 g.), which crystallised on the addition of light petroleum (b. p. 40—60°). Dry ammonia was passed into a solution of the crude disulphonyl chloride (m. p. 40—45°; 8·1 g.) in dry benzene (100 c.c.) with external cooling. When precipitation was complete excess of ammonia was removed with dry air, and the benzene was distilled off under reduced pressure. From the residue acetone extracted propane-1 : 3-disulphonamide (3·4 g.), which crystallised from aqueous acetone in needles, m. p. 172·5—174·5° (Found: N, 13·7. Calc. for $C_3H_{10}O_4N_2S_2$: N, 13·9%). Autenrieth and Bölli (*Ber.*, 1925, **58**, 2149) record m. p. 165° and Clutterbuck and Cohen (*loc. cit.*) m. p. 169° for this compound.

In similar manner the following compounds were prepared: *butylene*-1 : 4-*bisthiuronium bromide* (98% yield) in prisms, m. p. 208—210°, from water (Found: C, 20·0; H, 4·6; N, 15·1. $C_6H_{16}N_4Br_2S_2$ requires C, 19·6; H, 4·4; N, 15·2%); butane-1 : 4-disulphonyl chloride (80% yield) in needles, m. p. 83—84·5°, from benzene–light petroleum (cf. Helferich and Grünert, *loc. cit.*); butane-1 : 4-disulphonamide (60% yield) in plates, m. p. 179·5—180·5°, from hot water (cf. Helferich and Grünert, *loc. cit.*); NN′-*diacetylbutane*-1 : 4-*disulphonamide* in plates, m. p. 195·5—197·5°, from 95% alcohol (Found: C, 32·3; H, 5·1; N, 9·0. $C_8H_{16}O_6N_2S_2$ requires C, 32·0; H, 5·3; N, 9·3%); *pentylene*-1 : 5-*bisthiuronium bromide* (88% yield) in prisms, m. p. 159·5—161·5°, from alcohol (Found: C, 22·4; H, 5·0; N, 14·5. $C_7H_{16}N_4Br_2S_2$ requires C, 22·0; H, 4·7; N, 14·7%); pentane-1 : 5-disulphonyl chloride (88% yield) in needles, m. p. 67—69°, from benzene–light petroleum (cf. Clutterbuck and Cohen, *loc. cit.*); pentane-1 : 5-disulphonamide (60% yield) in needles, m. p. 131—133°, from aqueous alcohol (cf. Clutterbuck and Cohen, *loc. cit.*); NN′-*diacetylpentane*-1 : 5-*disulphonamide* in needles, m. p. 149·5—150·5°, from alcohol (Found: C, 34·3; H, 5·6; N, 9·2. $C_9H_{18}O_6N_2S_2$ requires C, 34·4; H, 5·7; N, 8·9%); *decylene*-1 : 10-*bisthiuronium bromide* (89% yield) in needles, m. p. 158·5—160·5°, from acetic acid (Found: C, 31·6; H, 6·0. $C_{12}H_{28}N_4Br_2S_2$ requires C, 31·85; H, 6·2%); *decane*-1 : 10-*disulphonamide* (63% yield from dithiuronium bromide) in plates, m. p. 162·5—164·5°, from acetic acid (Found: C, 40·5; H, 8·4; N, 9·2. $C_{10}H_{24}O_4N_2S_2$ requires C, 40·0; H, 8·0; N, 9·3%); NN′-*diacetyldecane*-1 : 10-*disulphonamide* in plates, m. p. 157·5—158·5°, from alcohol (Found: C, 43·8; H, 7·4; N, 7·3. $C_{14}H_{28}O_6N_2S_2$ requires C, 43·8; H, 7·3; N, 7·3%).

Pentylene-1 : 5-*bis-sulphonylguanidine* (cf. Birtwell *et al.*, *loc. cit.*).—Guanidine nitrate (5·6 g.)

was added to a solution of sodium hydroxide (1·84 g.) in hot methyl alcohol (12 c.c.) and after 15 minutes the mixture was cooled to 20° and the sodium nitrate filtered off and washed with methyl alcohol. Pentane-1 : 5-disulphonamide (5 g.) was added to the filtrate kept at 50—55° and, after removal of the methyl alcohol, *cyclo*hexanol (30 c.c.) was added and the temperature raised to 180—190° and kept thereat for 3 hours. When cold, hot benzene (25 c.c.) was added and, after warming, the upper layer was removed by decantation. The residue was dissolved in a minimum of hot water and the solution was cooled, and made just acid with 1·5N-hydrochloric acid and then just alkaline with 1·5N-sodium hydroxide. On scratching and cooling *pentylene*-1 : 5-*bis*-*sulphonylguanidine* (1·6 g.) separated, which crystallised from aqueous alcohol in needles, m. p. 190·5—191·5° (Found : C, 27·4; H, 5·6; N, 27·2. $C_7H_{18}O_4N_6S_2$ requires C, 26·8; H, 5·7; N, 26·8%).

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643. *Some Physical Investigations of the Behaviour of Bacterial Surfaces. Part I. The Electrophoretic Mobility of* Aerobacter aerogenes.

By P. J. BARRY and A. M. JAMES.

The electrophoretic mobility of a strain of *Aerobacter aerogenes*, grown in a synthetic medium, has been determined in a phosphate buffer solution of constant ionic strength. The mobility, and hence the charge density, of a 24-hour culture was found to be reproducible on repeated sub-culture over a period of 6 months. Nevertheless, variation of either the ionic strength or the pH value of the test solution brought about marked changes in the mobility. Killing the organisms with formaldehyde had no effect, but steaming the culture for different times caused pronounced changes in the mobility. A preliminary investigation has shown that the mobility of the organism remained constant throughout the growth cycle.

THE study of the electrophoretic mobility of a strain of *Aerobacter aerogenes* has been made in an attempt to correlate changes in growth characteristics with changes in mobilities and hence possible modifications of the cell surface. The literature contains many references to electrophoretic studies of different bacteria; but the variation of strain with the consequent change in growth conditions, and the different conditions of test, make any complete interpretation of the results difficult. *Aerobacter aerogenes* was chosen because, first, it has no exacting nutritional requirements, being readily cultured in a simple synthetic medium and, secondly, a careful study has already been made of its growth characteristics under different conditions (Hinshelwood, "Chemical Kinetics of the Bacterial Cell," Oxford, 1946).

The size and shape of bacteria vary considerably during the growth phase (Topley and Wilson, "Principles of Bacteriology and Immunity," 1946, E. Arnold & Co., London, p. 84) and we have observed a marked change in size with change of medium. Abramson and Michaelis (*J. Gen. Physiol.*, 1929, **12**, 587) and Abramson (*J. Phys. Chem.*, 1931, **35**, 289), however, found that the mobility of particles was independent of their size and shape within the limits of experimental error. This is in accord with the Helmholtz and the Smoluchowski theory that :

$$\text{electrophoretic mobility} = \bar{v} = v/E = \zeta\varepsilon/4\pi\eta$$

where ζ is the potential at the interface, and v the velocity of the particle under a field strength E in a medium of dielectric constant ε and viscosity η.

The mobility of *Escherichia coli* is independent of pH value over the pH range 4·0—7·0 in buffer solutions of constant ionic strength (Moyer, *J. Bact.*, 1936, **32**, 433), but a marked change of mobility accompanies variation of the ionic strength of the suspension

medium, similar to that observed for true colloidal particles (Robuschi, *Chem. Abs.*, 1947, 2114).

Moyer (*loc. cit.*) found no detectable change in the mobility of the organisms after repeatedly washing them with 0·0067M-phosphate buffer solution; Pedlow and Lisse (*J. Bact.*, 1936, **31**, 235), on the other hand, found some changes on washing *Esch. coli* grown in peptone broth containing added electrolytes.

This paper describes the standardisation of our technique and the determination of the mobility of a standard suspension. In this standardisation we have considered the possible variations of the mobility with the physical conditions of test, such as field strength, pH value, and ionic strength of the test solution, and with repeated washing.

The Mobility of Aerobacter aerogenes *grown in a Synthetic Medium.*—(a) *The mobility of a 24-hour culture.* The strain was sub-cultured regularly when full grown and in the first instance the mobility of a 24-hour-old culture was studied. The culture was harvested by centrifugation at 3000 r.p.m. and washed twice with 0·0067M-phosphate buffer solution (pH = 7·00; ionic strength = 0·013). The cells were re-suspended in the phosphate buffer to give a final suspension of approximately 10^8 organisms/ml., and the average velocity was determined under a constant field strength. The field strength was altered

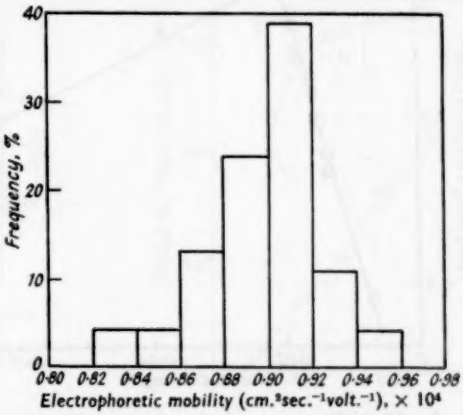


FIG. 1. *Histogram of the electrophoretic mobility of* Aerobacter aerogenes. *(All mobilities are to be understood as being towards the positive electrode.)*

and the velocity again determined, thus enabling a certain amount of personal error to be eliminated. From Table 1 it is seen that the mobility is independent of the field strength, within the limits of experimental error.

Repeated sub-culture of the organisms over a period of months showed that the mobility of a 24-hour culture was constant at $0{\cdot}90 \pm 0{\cdot}01 \times 10^{-4}$ cm.^{2}sec.$^{-1}$volt.$^{-1}$ (standard deviation $\pm 0{\cdot}03$). Fig. 1 shows the distribution of the mobilities in about 50 separate determinations carried out over a period of 6—7 months, each determination being the mean of 10 observations of an individual cell. It can be seen that the cultures investigated

TABLE 1. *Effect of field strength on the electrophoretic mobility.*

Field strength (volt/cm.)	10·95	12·77	13·68	13·85	15·66
Velocity at 25° (cm./sec.), × 10^4	10·12	11·53	12·14	12·38	14·30
Electrophoretic mobility (cm./sec./volt./cm.), × 10^4 ...	0·92	0·90	0·88	0·89	0·91

were of a single population, showing an approximate Gaussian distribution about the mean. The organisms carry a negative charge corresponding to a ζ potential of $-0{\cdot}011$ v and a charge density of 860 e.s.u.

The mobility of such washed suspensions remained constant for periods of up to 24 hours when stored at 40°, at room temperature, or in the ice-chest, as previously shown by Dozois and Hachtel (*J. Bact.*, 1935, **30**, 473).

The effect on the mobility of repeatedly washing with phosphate buffer was studied to establish whether there is any change on the cell surface. The mobilities of 24-hour

cultures determined after each washing (Table 2) indicate that there is no modification of the cell surface under this treatment, in agreement with Moyer's observations on *Esch. coli* (*J. Bact.*, 1936, **32**, 433). Nevertheless, the standard technique adopted by us for all future work was to wash the cells twice with phosphate buffer solution.

TABLE 2. *Effect of washing on the electrophoretic mobility.*

Number of washings	0	1	2	3
Electrophoretic mobility (cm./sec./volt/cm.), $\times 10^4$ ...	0·88	0·87	0·88	0·87

Killing the organisms with formaldehyde solution had no influence on the mobility, whilst boiling the culture had a pronounced but variable effect. A 24-hour culture was divided into five portions and treated as follows: (i) centrifuged and washed twice—control; (ii) formaldehyde added to give a final concentration of 5%, set aside for 10 minutes, centrifuged, and washed twice with phosphate buffer; (iii), (iv), and (v) culture heated in steam for 15, 60, and 120 minutes, respectively, centrifuged, and

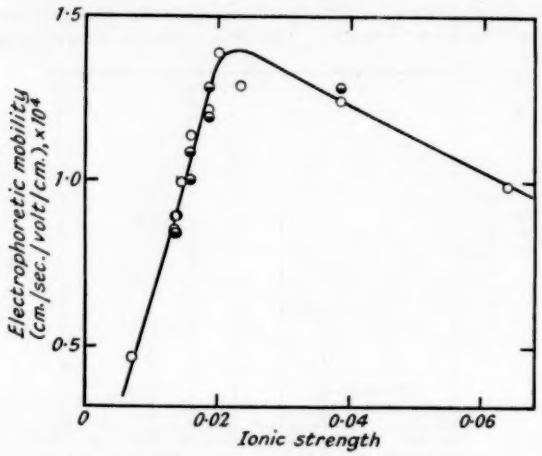


FIG. 2. *Variation of the electrophoretic mobility of* Aerobacter aerogenes *with the ionic strength of the test solution. (Open circles—24-hour culture, half-shaded circles—culture at the end of growth phase.)*

washed. Viability tests of the five portions were made on agar plates. The results (Table 3) are in agreement with those obtained for *Esch. coli* and *Corynebacterium diphtheriae* (Dozois and Hachtel, *loc. cit.*; Buggs and Green, *J. Bact.*, 1935, **30**, 453).

TABLE 3. *Effect of formaldehyde and steaming on the electrophoretic mobility.*

Treatment	Electrophoretic mobility (cm./sec./volt./cm.), $\times 10^4$ observed	average	Viability
Control	0·89, 0·87, 0·89	0·88	+++
5% Formaldehyde	0·88, 0·87, 0·89	—	—
	0·90, 0·87, 0·88	0·88	—
15 Minutes' steaming	0·83, 0·80	0·82	—
60 Minutes' steaming *	0·67, 0·69	0·68	—
120 Minutes' steaming *	0·82	0·82	—

* Difficulty was encountered with these cultures as the organisms coagulated and were only re-suspended by shaking them for a long time.

(b) *Variation of the mobility with the ionic strength of the test solution.* A 24-hour-old culture was harvested, washed twice with 0·0067M-phosphate buffer solution, and suspended in phosphate buffer solutions (pH = 7·00) containing varying amounts of sodium chloride to increase the ionic strength. The mobilities determined in these solutions are shown in Fig. 2. The mobilities of cultures harvested at the end of the logarithmic growth phase were the same as those of older cells, indicating no detectable difference in the surface behaviour of old and young cells (Fig. 2). (Results obtained several months later were

in complete agreement with those of the main experiments, thus emphasising the reproducibility of the technique.)

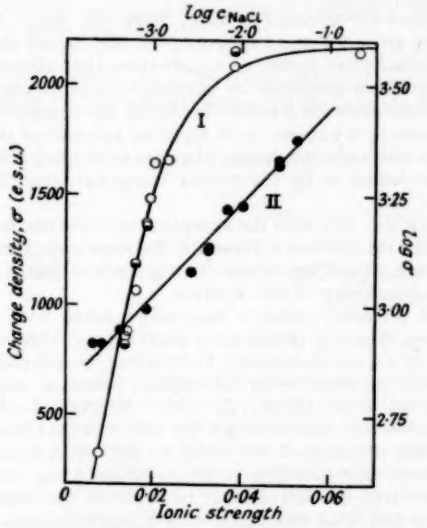
This behaviour was shown to be reversible, since cells washed free from the added salt and re-suspended in the normal phosphate buffer solution had the mobility of untreated cells.

The charge density on the organisms at different ionic strengths was calculated from the equation :

$$\sigma = 17{,}600[\Sigma c_i(e^{-z_i\zeta/0\cdot0256} - 1) + \Sigma c_j(e^{+z_j\zeta/0\cdot0256} - 1)]^{\frac{1}{2}}$$

where c_i and c_j are the ionic concentrations and z_i and z_j the valencies of the positive and negative ions, respectively (Abramson and Moyer, *J. Gen. Physiol.*, 1936, **19**, 601). Fig. 3, curve I, shows the charge density plotted as a function of the ionic strength.

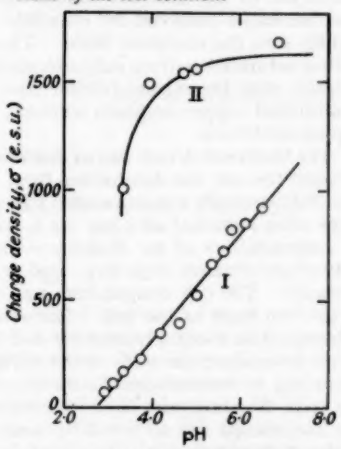
FIG. 3.



Curve I. *Variation of the charge density of* Aerobacter aerogenes *with the ionic strength of the test solution. (Open circles—24-hour culture, half-shaded circles—culture at end of growth phase.)*

Curve II. log σ *plotted against* log c_{NaCl} *(calculated from curve I).*

FIG. 4. *Variation of the charge density of* Aerobacter aerogenes *with the* pH *value of the test solution.*



Curve I. *At different ionic strengths.*
Curve II. *At constant ionic strength.*

(c) *Variation of the mobility with the* pH *value of the test solution.* The buffer solutions used, in the first instance, were made from suitable mixtures of 0·0067M-disodium hydrogen phosphate and 0·0033M-citric acid (McIlvaine, *J. Biol. Chem.*, 1921, **49**, 183), and their pH values determined. A 24-hour culture was centrifuged, washed twice with the appropriate buffer solution, and re-suspended in that solution for the mobility determination. The results, Fig. 4, curve I, show that below pH 7·5 the charge density is a linear function of pH; observations above pH 7·5 indicated little change. The experiment was repeated with cells harvested at the end of the logarithmic growth phase, but again, no significant difference could be detected between the behaviour of old and young cells.

The ionic strengths of these buffer solutions increased from approximately 0·0015 at pH 3·0 to 0·02 at pH 6·5, so the variation of charge density is possibly due to change of ionic strength as well as pH. The experiment was repeated with the addition of sodium chloride to bring the total ionic strength up to 0·02 (cf. normal value 0·013). The charge density at constant ionic strength is independent of pH between pH 7·0 and pH 4·0, but below pH 4·0 there is a marked decrease (Fig. 4, curve II).

Experimental

Cultures and Media.—The strain of *Aerobacter aerogenes*, originally obtained from the National Collection of Type Cultures (Hinshelwood and Lodge, *J.*, 1939, 1683), has been maintained by monthly sub-culture in veal bouillon. For test purposes the organism was grown in a sterile synthetic medium containing glucose (19·2 g./l.), potassium dihydrogen phosphate (3·46 g./l.), ammonium sulphate (0·96 g./l.), and magnesium sulphate (0·04 g./l.), adjusted to pH 7·12 with 4N-sodium hydroxide. The strain was sub-cultured daily in this synthetic medium at 40° in the presence of a slow stream of washed sterile air. In this medium the organism had a mean generation time (*i.e.* the time required for the number of cells to double during the logarithmic growth phase) of 32—34 minutes, which would indicate that the strain had undergone no apparent mutation during the past years. The growth was determined by measuring the turbidity of formaldehyde-killed samples with a Hilger photoelectric absorptiometer, which had been calibrated against hæmocytometer counts (Monod, " La Croissance des Cultures Bactériennes," Paris, Hermann & Cie., 1942).

The Electrophoretic Cell.—This was as described by Moyer (*J. Bact.*, 1936, **31**, 531). It consisted of two Hysil optically flat plates (25 × 40 × 0·5 mm.) mounted 0·5 mm. apart and connected to the electrode compartments by ground-glass joints, a modification that allowed the cell to be removed for cleaning. The plugs were prepared by packing a plaster paste tightly into the electrode limbs. These plugs were made to conduct by filling the apparatus with a saturated sodium sulphate solution and passing a current, with repeated reversal of the polarity until the current became constant. The electrode compartments were then filled with a saturated copper sulphate solution, which was sealed in by the rubber bungs carrying the copper electrodes.

The electrical circuit was as described by Moyer (*loc. cit.*) with the exception that the current through the cell was determined from the potential drop across a standard 200-ohm resistance. The field strength was calculated from the equation, $E = I/\kappa q$, where I is the current (amps.), q the cross-sectional area (sq. cm.), and κ the conductivity of the solution.

Determination of the Mobility.—The cell was mounted under a microscope fitted with a ×40 phase-contrast objective, used in conjunction with a ×10 eye-piece carrying a calibrated graticule. The cell temperature was measured by copper–constantin thermocouples attached to the two faces of the cell. The velocities of the particles under the applied potential were determined at room temperature and then corrected to 25° (Moyer, *loc. cit.*). In the flat cell, liquid flows along the walls of the cell in one direction and back through the centre in the other. According to Smoluchowski's theory, provided that the ratio of cell width to cell depth is not less than 20, stationary liquid layers occur at depth fractions of 0·21 and 0·79 down the cell. The microscope was adjusted by means of a calibrated fine adjustment to focus on the lower of the stationary levels. Any particle in focus at this level was timed over a known distance (usually 0·012 cm.) across the graticule first in one direction and then in the other, thus eliminating any slight differences between the two electrodes. At least ten particles were timed in both directions under a constant field strength to give an average velocity, from which the electrophoretic mobility was calculated.

Calibration of the Cell.—The electrophoretic mobility of mammalian erythrocytes is independent of the age, sex, colour, and blood group of the donor. The value of this mobility, which in 0·067M-phosphate buffer solution (pH 7·35) is $1{\cdot}31 \times 10^{-4}$ cm./sec./volt/cm. (Abramson, *J. Gen. Physiol.*, 1929, **12**, 711), was used to calibrate the electrophoresis cell.

Discussion

It has been demonstrated that the electrophoretic technique described above gives reproducible results when applied to bacterial suspensions prepared under standard conditions over a period of 6 months. Further, the mobility of the bacterial culture has remained constant over the same period when grown under the specified conditions. Washed-cell suspensions retained over a period of 24 hours also gave a constant mobility. On the other hand, cultures that have been steamed for 15 minutes showed a marked change in mobility, presumably due to cell disorganisation.

The charge density of the organisms has, however, been shown to be sensitive to changes in the ionic strength of the suspension medium, indicating that extreme care must be exercised to control this factor. Thus, as pointed out by Moyer (*J. Bact.*, 1936, **32**, 433), mobilities determined in water should be regarded as unsatisfactory since here the ionic

strength is an uncontrollable factor. The behaviour of the bacterial particles towards ionic-strength changes follows a curve similar to that expressed in the simple Langmuir adsorption isotherm $\sigma = kc^{1/n}$ where c is the electrolyte concentration, and k and n are constants. This is further borne out by Fig. 3, curve II, which shows a linear relation between log σ and log c; this is a general characteristic of colloidal particles.

The surface is relatively insensitive to changes in hydrogen-ion concentration over a wide range, indicating the absence of protein as a primary surface constituent. The observation that death incurred by treatment with formaldehyde is without effect on the mobility, further supports this inference. Abramson came to a similar conclusion regarding the surface of *Esch. coli*.

It has also been found that no detectable difference exists between young cells, harvested at the end of the growth phase, and those harvested several hours later. This observation suggests that the nature of the surface does not change either during active cell division or during ageing in the growth medium; this aspect is to be considered in more detail in a later paper.

The authors gratefully acknowledge a grant from the Chemical Society which defrayed the cost of the cell and the phase-contrast equipment.

CHELSEA POLYTECHNIC, LONDON, S.W.3. [*Received, May 6th*, 1952.]

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644. *Infra-red Spectroscopy and Structural Chemistry. Part III.* Gladiolic Acid.*

By JOHN FREDERICK GROVE.

The infra-red spectroscopic methods for the study of keto–lactol tautomerism described in Part I (*J.*, 1951, 877) are applied in the present paper to the mould metabolic product gladiolic acid and its derivatives. The conclusions reached are compared with those obtained from an examination of the ultra-violet absorption data for the same compounds in solution. Whereas gladiolic acid and its dibasic oxidation product, $C_{11}H_{10}O_6$, are present in the lactol form in the solid state, an equilibrium between the lactol and the open-chain form exists in aqueous solution, the pH being the determining factor. The esters of gladiolic acid prepared by Grove (*Biochem. J.*, 1952, **50**, 648) are shown to be *pseudo*-esters; and some points of interest in connection with the correlation of absorption frequency with chemical structure are discussed.

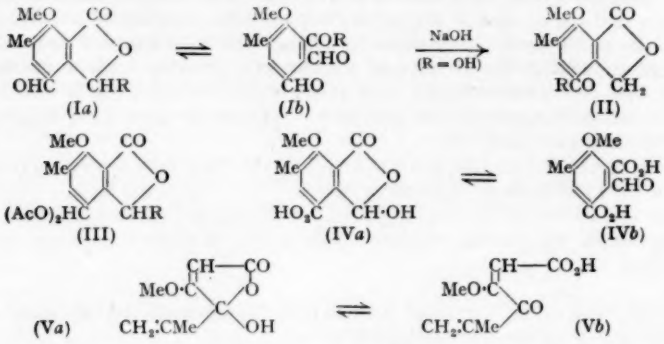
IN Part I of this series, Grove and Willis (*J.*, 1951, 877) discussed some of the factors governing the use of infra-red spectroscopy in the study of keto–lactol tautomerism, and showed that the open-chain and the lactol forms of aldehydic and ketonic acids could be recognised by the presence of certain characteristic bands. In addition, it was found that the observed frequencies of the stretching vibrations of the C=O groups could be used to distinguish between normal and *pseudo*-esters of γ-aldehydic and ketonic aicds.

Gladiolic acid, $C_{11}H_{10}O_5$, an antifungal metabolic product of *Penicillium gladioli* Machacek, was first described by Brian, Curtis, Grove, Hemming, and McGowan (*Nature*, 1946, **157**, 697) and was shown to have the structure (I; R = OH) in two papers published simultaneously from these laboratories (Grove, *Biochem. J.*, 1952, **50**, 648) and from the London School of Hygiene (Raistrick and Ross, *ibid.*, p. 635).

Both gladiolic acid and its dibasic oxidation product, $C_{11}H_{10}O_6$ (IV), show keto–lactol tautomerism in solution, under the influence of chemical reagents, and it was of interest to discover the precise structures of these compounds in the solid state. The esters of gladiolic acid described by Grove (1952, *loc. cit.*) were considered to be *pseudo*-esters both

* Part II, Grove, *J.*, 1951, 883.

from their method of preparation and from their chemical properties; their structures are important from the point of view of the correlation of chemical structure with biological activity and a proof of their constitution was desirable.



The present paper deals with the application to gladiolic acid and its derivatives of the infra-red spectroscopic methods described in Part I; in addition, a number of features of interest in connection with the correlation of chemical structure and absorption frequency are discussed.

Experimental

M. p.s are corrected. Microanalyses are by Drs. Weiler and Strauss, Oxford.

Infra-red Spectra.—These were obtained by using the modified Hilger D 209 instrument described by Grove and Willis (*loc. cit.*). With the exception of gladiolic acid hemihydrate and penicillic acid hydrate, solid compounds were first dried *in vacuo* over phosphoric oxide. All solid compounds were examined in "Nujol" suspension between rock-salt plates. The suspensions were made by grinding the solids to fine powders in an agate mortar and then stirring the powder with "Nujol." Liquids indicated in Table 1 by an asterisk were examined in a cell of 0·01-mm. thickness. Energy backgrounds were obtained in absence of the sample, and the percentage absorption curves for the region 700—1900 cm.$^{-1}$ plotted in the usual way. Two of the curves are reproduced in Fig. 1. Owing to variations in the thickness of the suspensions used, it is not possible to compare intensities of the absorption bands in the spectrum of one compound with those in another.

Ultra-violet Spectra.—These were obtained by using a Hilger medium quartz spectrograph in conjunction with a "Spekker" ultra-violet spectrophotometer. A hydrogen discharge tube was used as light source, and the concentrations of the solutions were adjusted so that the values of $\log_{10} I_0/I$ between 0·3 and 1·0 were obtained for the absorption peaks with a path length of 0·1 cm.

The data on penicillic acid were obtained with a Unicam S.P. 500 quartz spectrophotometer; this instrument was also used to check some of the results obtained by the older technique. With the Unicam instrument the complete absorption curve was available within 30 minutes of making up the solution, compared with approx. 2 hours in the case of the photographic method.

Materials.—Details of the purification of gladiolic acid and of the preparation of most of the derivatives studied are given by Grove (1952, *loc. cit.*).

Gladiolic acid hemihydrate. Gladiolic acid was allowed to crystallise slowly from a large volume of water, and the colourless prisms of the *hemihydrate*, m. p. 155°, were dried *in vacuo* at room temperature over concentrated sulphuric acid (Found: C, 57·3, 57·2; H, 5·0, 4·9; OMe, 13·8%; equiv., 228. $C_{11}H_{10}O_5,\frac{1}{2}H_2O$ requires C, 57·1; H, 4·8; 1OMe, 13·4%; equiv., 231). The water of crystallisation was readily lost at 100° *in vacuo* over phosphoric oxide and the infra-red spectrum of the dried material was identical in the double-bond stretching region with that of anhydrous gladiolic acid (Found, on a specimen dried for 6 hours as above: C, 59·7; H, 4·4; OMe, 14·6%; equiv., 207. Calc. for $C_{11}H_{10}O_5$: C, 59·45; H, 4·5; 1OMe, 14·0%; equiv., 222).

Esterification of gladiolic acid hemihydrate with methanol under Fischer–Speier conditions gave methyl gladiolate, m. p. and mixed m. p. with an authentic sample, 138° (Found: C, 61·05; H, 5·1; OMe, 26·7. Calc. for $C_{12}H_{12}O_5$: C, 61·0; H, 5·1; 2OMe, 26·2%).

Sodium gladiolate hydrates. Aqueous sodium hydroxide (0·108N; 10·50 ml.) was added to gladiolic acid (0·25 g.) in ethanol (4 ml.), and the resulting solution evaporated to dryness *in vacuo* at room temperature. The solid obtained crystallised from aqueous acetone in colourless needles (dried *in vacuo* at room temperature over sulphuric acid) of *sodium gladiolate trihydrate* (Found: C, 44·7; H, 4·6. $C_{11}H_9O_5Na,3H_2O$ requires C, 44·3; H, 5·0%). Further drying for 4 hours at 100° *in vacuo* over phosphoric oxide gave the *dihydrate*, colourless needles, m. p. 230° (decomp.) (Found: C, 46·8; H, 4·9; OMe, 11·3. $C_{11}H_9O_5Na,2H_2O$ requires C, 47·1; H, 4·7; OMe, 11·1%). When heated slowly, the trihydrate decomposed at the decomposition point of the dihydrate; but, when heated suddenly to 180°, the trihydrate melted, reset, and finally melted (with decomp.) at 230°. The infra-red spectra of the two hydrates were very similar, and differed only in the relative intensities of some of the absorption bands. Both the di- and the tri-hydrate of sodium gladiolate gave an immediate precipitate with Brady's reagent

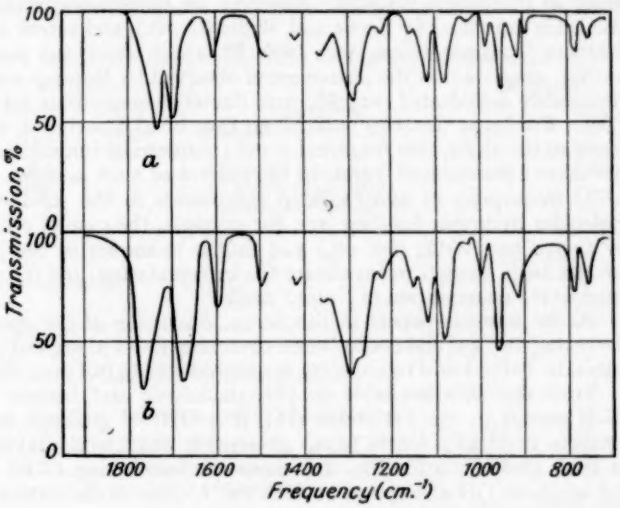


FIG. 1.
a, Gladiolic acid.
b, Gladiolic acid hemihydrate.

in ethanol and after solution in dilute acetic acid gave an intense green colour on the addition of excess of ammonia solution (*d* 0·880). Unlike gladiolic acid, the hydrated sodium salts did not become greenish-brown when suspended in air for a few seconds over ammonia solution (*d* 0·880), and on treatment with ammonia solution (without previous addition of acetic acid) the greenish-brown colour developed only very slowly.

Addition of concentrated hydrochloric acid to an aqueous solution of sodium gladiolate dihydrate gave a colourless precipitate, m. p. and mixed m. p. with gladiolic acid, 158—160°.

When sodium gladiolate dihydrate was dried for 8 hours *in vacuo* over phosphoric oxide at 140° the *monohydrate* was obtained as a yellow solid, m. p. 200—204° (decomp.) (Found: C, 50·5; H, 3·7. $C_{11}H_9O_5Na,H_2O$ requires C, 50·4; H, 4·2%). The material was hygroscopic and it is possible that some decomposition may have taken place during the drastic drying; for these reasons the infra-red spectrum was not examined. The crude monohydrate gave the intense green colour with acetic acid and ammonia solution.

Penicillic acid. The monohydrate, m. p. 64—65°, was obtained by recrystallisation of the crude acid from water (Found, on air-dried material: C, 51·4; H, 6·7. Calc. for $C_8H_{10}O_4,H_2O$: C, 51·1; H, 6·4%). Drying *in vacuo* over phosphoric oxide for 24 hours at room temperature gave the anhydrous acid, m.p. 85° (Found: C, 56·7; H, 5·9. Calc. for $C_8H_{10}O_4$: C, 56·5; H, 5·9%).

Phthalaldehyde. When prepared from *o*-xylene by known methods and crystallised from light petroleum (b. p. 40—60°), this had m. p. 54°.

Results and Discussion

Although the interpretation of the infra-red absorption spectra of organic compounds is generally more reliable when the substances are examined in solution in a non-bonding solvent, Grove and Willis (*loc. cit.*) pointed out the advantages to be obtained from the examination of the spectra of crystalline samples in the study of keto–lactol tautomerism. These are, first, that since carboxylic acids are wholly in the dimeric form in the solid state, the characteristic stretching frequencies of alcoholic –OH and carboxylic acid –OH groups, and of lactone ring and carboxylic acid C=O groups, are more widely separated and hence more readily identified; and, secondly, that the spectra of carboxylic acids are not complicated by the presence of both monomeric and dimeric forms. Nevertheless, some workers have been critical of the use of Nujol " mulls " in an investigation of this kind. Munday (*Nature*, 1949, **163**, 443) claimed that the keto-acid form (V*b*) of penicillic acid was converted into the lactol form (V*a*) by the ordinary procedure of grinding in Nujol and this very naturally raised doubts about the usefulness of the technique in the study of tautomeric systems. However, no analogous effects were observed with any of the acids examined by Grove and Willis (*loc cit.*), and recent work by Ford, Johnson, and Hinman (*J. Amer. Chem. Soc.*, 1950, **72**, 4529), which has been confirmed by the present author, suggests that the phenomenon observed by Munday was actually the conversion of the readily dehydrated penicillic acid (lactol) monohydrate into the anhydrous lactol form (V*a*). Ford *et al.* (*loc. cit.*) pointed out that bond association in crystalline samples affects many of the absorption frequencies and considered it undesirable to base interpretations on the actual positions of bands in the spectra of such samples. Whilst it is true that the C=O frequencies of hydroxylated compounds in the solid state are affected by intermolecular hydrogen bonding [see, for example, the case of *o*-formylbenzoic acid discussed by Grove and Willis (*loc. cit.*) and similar examples in the present paper], these shifts are not large enough to invalidate the interpretation, and the present investigation is confined to the examination of Nujol " mulls."

As in previous papers in this series, discussion of the spectra is limited to the –OH stretching (3—4 μ) and double-bond stretching (5—7 μ) regions; the relevent data are contained in Table 1 and two spectra are reproduced in full over the range 5—14 μ in Fig. 1.

From the data available on phthalaldehyde and benzoic acid (Table 1), the three C=O groups in the keto-form (I*b*; R = OH) of gladiolic acid might be expected to combine to yield a single broad absorption band with maximum at about 1685 cm.$^{-1}$. In fact, gladiolic acid (Fig. 1*a*) shows phthalide ring C=O absorption at 1733 cm.$^{-1}$ and alcoholic OH absorption at 3225 cm.$^{-1}$, close to the values found for *o*-formylbenzoic acid (3-hydroxyphthalide) (Part I), and obviously exists in the lactol form (I*a*; R = OH) in the solid state. The band at 1700 cm.$^{-1}$ in the gladiolic acid spectrum is attributed to the C=O of the formyl substituent; the frequency is slightly higher than that found in benzaldehyde, the difference being due to the resultant electronic effect of the additional substituents. The phthalide ring C=O frequency in *o*-formylbenzoic acid is some 15 cm.$^{-1}$ lower than that found in phthalide itself and this lowering was attributed by Grove and Willis (*loc. cit.*) to intermolecular hydrogen bonding. A similar lowering of the normal C=O and OH frequencies is found with gladiolic acid and suggests intermolecular hydrogen bonding between the phthalide ring C=O groups and lactol OH groups of adjacent molecules. This hypothesis receives considerable support from the results obtained with gladiolic acid hemihydrate in which two molecules of gladiolic acid, instead of being directly associated, are presumably linked through a molecule of water. The spectra of gladiolic acid and its hemihydrate (Fig. 1*b*) are almost identical, except in the C=O and OH stretching regions. The phthalide ring C=O frequency in the hemihydrate appears close to the expected value, 1760 cm.$^{-1}$ (the increase of 10 cm.$^{-1}$ over the normal phthalide figure being due to the substituents attached to the benzene nucleus [cf. deoxygladiolic acid (I*a*; R = H) (Table 1) which absorbs at 1758 cm.$^{-1}$], but the formyl C=O frequency appears at 1680 cm.$^{-1}$, a lowering of 20 cm.$^{-1}$ compared with gladiolic acid. It follows that the molecules of gladiolic acid in the hemihydrate are associated through the water molecule by intermolecular hydrogen bonding involving the formyl groups. The hemihydrate shows two

absorption bands due to OH stretching vibrations in the 3-μ region, at 3495 and 3185 cm.$^{-1}$. It may be presumed that the 3495-cm.$^{-1}$ band arises from the " free " lactol OH groups [*e.g.*, phthalonic acid (3-hydroxyphthalide-3-carboxylic acid), in which dimerisation takes place through the carboxyl group, shows lactol OH absorption at 3470 cm.$^{-1}$, Part I], whilst that at 3185 cm.$^{-1}$ comes from the water molecules involved in hydrogen bonding, although there is no proof of these assignments. Gladiolic acid hemihydrate is readily converted into the anhydrous compound by drying *in vacuo* over phosphoric oxide. In view of Munday's results with penicillic acid it was of interest to see whether the hemihydrate could be converted into anhydrous gladiolic acid by the ordinary procedure of grinding with " Nujol " : the spectra of both gladiolic acid and its hemihydrate were totally unaffected by 10 minutes' grinding with " Nujol " under the conditions normally employed in the preparation of the specimens.

The dibasic acid, $C_{11}H_{10}O_6$ (IV), obtained by oxidation to carboxyl of the formyl group of gladiolic acid which does not take part in keto–lactol tautomerism, shows alcoholic OH absorption at 3390 cm.$^{-1}$ and a phthalide ring C=O frequency at 1760 cm.$^{-1}$, and exists in the lactol form (IV*a*) in the solid state. As might be expected from the similarity

TABLE 1. *Infra-red absorption data for gladiolic acid and its derivatives.*

Compound	Frequency C=O	Frequency OH	Compound	Frequency C=O	Frequency OH
Benzoic acid	1690	2620, 2540	Phthalide	1750	—
Phthalaldehyde	1680	—	*o*-Formylbenzoic acid	1738	3250
Benzaldehyde *	1695	—	*o*-Formylbenzoic acid, *pseudo*-methyl ester	1768	—

* Cf. p. 3346.

Compound	Frequency C=O	Frequency OH
Gladiolic acid (I; R = OH)	1733, 1700	3225
Gladiolic acid hemihydrate	1765, 1680	3495, 3185
Methyl gladiolate (I*a*; R = OMe)	1775, 1705	—
Ethyl gladiolate (I*a*; R = OEt)	1770, 1705	—
Acetylgladiolic acid (3-acetoxy-4-formyl-7-methoxy-6-methylphthalide) (I*a*; R = OAc)	1768, 1700	—
Triacetylgladiolic acid hydrate (3-acetoxy-4-diacetoxymethyl-7-methoxy-6-methylphthalide) (III; R = OAc)	1785, 1765	—
4-Diacetoxymethyl-3 : 7-dimethoxy-6-methylphthalide (III; R = OMe)	1765	—
Deoxygladiolic acid (4-formyl-7-methoxy-6-methylphthalide) (I*a*; R = H)	1758, 1695	—
*iso*Gladiolic acid (7-methoxy-6-methylphthalide-4-carboxylic acid) (II; R = OH)	1755, 1688	2630, 2560
Methyl *iso*gladiolate (methyl 7-methoxy-6-methylphthalide-4-carboxylate) (II; R = OMe)	1766, 1708	—
Oxidation product $C_{11}H_{10}O_6$ (3-hydroxy-7-methoxy-6-methylphthalide-4-carboxylic acid) (IV*a*)	1760, 1688	3390{2605, 2510
Penicillic acid (V)	1742	3280
Penicillic acid hydrate	1723	3400
Sodium gladiolate dihydrate	1580	3425—3125

in chemical structure, the spectrum is almost identical, in the range 5—14 μ, with that of *iso*gladiolic acid (II; R = OH), the compound obtained by rearrangement of gladiolic acid under alkaline conditions. In the dibasic acid, $C_{11}H_{10}O_6$, dimerisation takes place through the free carboxyl groups, and, as in the examples quoted above, the phthalide ring C=O and lactol OH frequencies (1760 and 3390 cm.$^{-1}$, respectively) appear close to the normal values.

Thus, while in the above examples there is a considerable variation in the observed values of the phthalide ring C=O and lactol OH frequencies, the interpretation of the results is not in doubt and gladiolic acid, its hemihydrate, and dibasic oxidation product are all in the lactol form in the solid state.

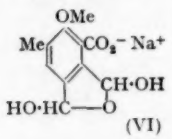
A somewhat similar picture is presented by penicillic acid and its hydrate. The anhydrous acid shows lactone ring C=O absorption at 1742 cm.$^{-1}$ and exists in the lactol form (V*a*); although the single C=O absorption band falls at 1723 cm.$^{-1}$ in the hydrate,

the general pattern of absorption bands in the double-bond stretching region is very similar to that found with the anhydrous material and is quite unlike that predicted for the keto form (V*b*) from data on αβ-unsaturated ketones and carboxylic acids (see Part I). Therefore, although the lactone C=O frequency has been lowered from 1742 to 1723 cm.$^{-1}$ in the hydrate by association with the water molecule, the interpretation of the results is clear and both the anhydrous acid and its hydrate exist in the lactol form (V*a*) in the solid state.

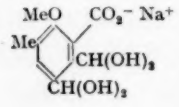
Grove (*loc. cit.*) reported the isolation of methyl and ethyl esters of gladiolic acid and although the chemical evidence, and in particular the formation of non-aldehydic diacetyl derivatives (of the hydrated formyl group), suggested that these compounds were *pseudo*-esters, the structures were not conclusively established. The bands at 1775 and 1770 cm.$^{-1}$ respectively in methyl and ethyl gladiolate may be compared with an absorption of similar frequency in the *pseudo*-methyl ester of *o*-formylbenzoic acid (Part I), and leave no further room for doubt that the compounds are *pseudo*-esters of structure (I*a*; R = OMe and OEt respectively).

Sodium gladiolate could not be obtained anhydrous. Its dihydrate was stable *in vacuo* at 100° over phosphoric oxide, and showed an intense absorption close to 6·3 μ, the maximum falling at 1580 cm.$^{-1}$ with an inflexion at 1612 cm.$^{-1}$ (a band of medium strength close to 1605 cm.$^{-1}$, due to the aromatic ring, is present in all gladiolic acid derivatives examined), and broad unresolved absorption (3425—3125 cm.$^{-1}$) in the OH stretching region. The band at 1580 cm.$^{-1}$ is attributed to the ionised carboxyl group (cf. Thompson, *J.*, 1948, 328) in the keto-form of gladiolic acid, and the absence of bands in the 5·5—6·0 μ region to the fact that sodium gladiolate dihydrate has either the bisdihydroxymethyl structure (VII) or the dihydroxyphthalan structure (VI) with 1 molecule of water of crystallisation.

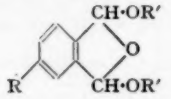
Seekles (*Rec. Trav. chim.*, 1923, **42**, 706) observed that phthalaldehyde formed a monohydrate in water and Weygand, Vogelbach, and Zimmerman (*Ber.*, 1947, **80**, 391) prepared 6-bromo-1 : 3-dimethoxyphthalan (VIII; R = Br, R′ = Me) by the action of methanol on 4-bromophthalaldehyde. It has not been possible to decide between (VI) and (VII),



(VI)



(VII)



(VIII)

the two possible structures for sodium gladiolate dihydrate; a molecule of water was removed from the dihydrate (this was accompanied by some decomposition) by prolonged drying *in vacuo* over phosphoric oxide at 140°, but the resulting material could not be recrystallised and was not investigated further.

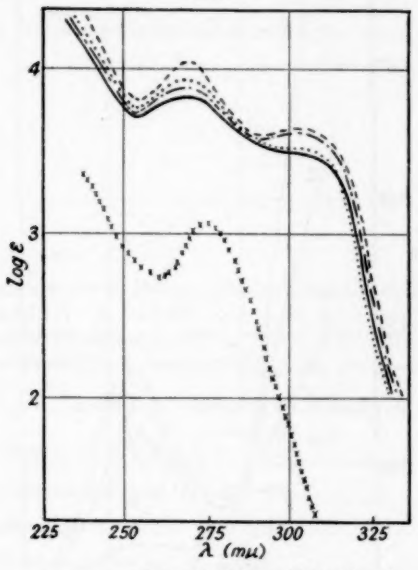
Gladiolic acid and its derivatives provide an interesting example of how structural changes in a series of related compounds can be followed in the infra-red spectra. Thus, acetylation of the lactol hydroxyl group in gladiolic acid to give (I*a*; R = OAc) leads to the disappearance of the OH stretching frequency at 3225 cm.$^{-1}$ and the phthalide ring C=O band moves from the " bonded " position at 1773 cm.$^{-1}$ to 1768 cm.$^{-1}$ (masking the C=O in the acetyl group introduced), whilst the formyl C=O frequency at 1700 cm.$^{-1}$ is unaffected. Acetylation of this group (in its hydrated form) eliminates the band at 1700 cm.$^{-1}$ and a new band appears at 1785 cm.$^{-1}$. A similar sequence can be traced in the formation of the diacetyl derivative of *pseudo*-methyl gladiolate (III; R = OMe). Deoxygladiolic acid (I*a*; R = H) shows phthalide ring and formyl C=O frequencies at 1758 and 1695 cm.$^{-1}$ as expected, and the latter band moves to 1688 cm.$^{-1}$ on oxidation of deoxygladiolic acid to *iso*gladiolic acid (II; R = OH), and to 1708 cm.$^{-1}$ in the normal ester, methyl *iso*gladiolate (II; R = OMe). Thus additional confirmation is provided of the structures allocated to these derivatives.

These structural changes can also be followed in the ultra-violet spectra although the interpretation of the results obtained with gladiolic acid is not straightforward. Fortun-

ately, however, *iso*gladiolic acid (II; R = OH) and the neutral deoxygladiolic acid (I*a*; R = H), in which there is no doubt about the chromophoric systems present, are available to act as models. With their aid the structures of the esters of gladiolic acid can be arrived at independently of the infra-red data and deductions can be made concerning the structure of the gladiolic acid molecule in solution. Without them, the interpretation is ambiguous and uncertain. The ultra-violet absorption data are given in Table 2 and the curves are plotted in Figs. 2 and 3.

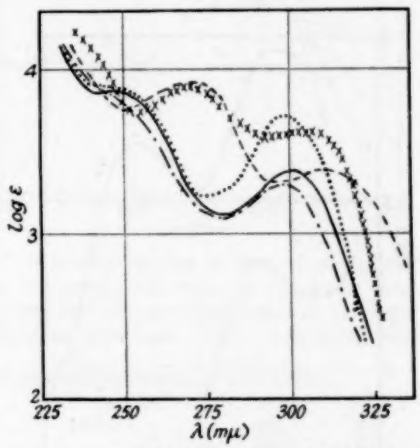
The curves for methyl and ethyl gladiolate and the neutral monoacetyl compound closely follow that for deoxygladiolic acid (I*a*; R = H) with two maxima at 305 and 269 mμ (Fig. 2), and these derivatives clearly have the *pseudo*-structures (I*a*; R = OMe, OEt, and OAc, respectively). Substitution of the formyl C=O chromophore of deoxygladiolic acid

FIG. 2.



—·—·— *Deoxygladiolic acid in ethanol.*
——— *Gladiolic acid in ethanol.*
– – – – – – ,, ,, *water.*
× × × × ,, ,, 0·1N-NaOH.
. . . . . *Ethyl gladiolate in ethanol.*

FIG. 3.



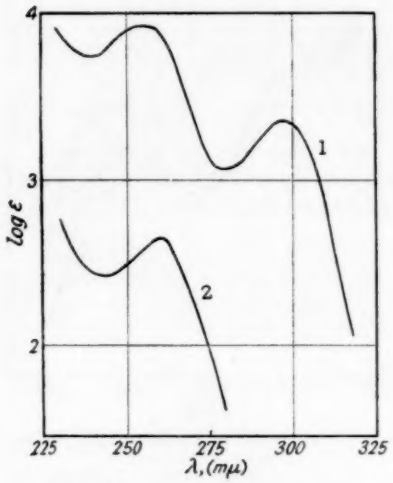
——— *Oxidation product* $C_{11}H_{10}O_6$ *in ethanol.*
—·—·— *Oxidation product* $C_{11}H_{10}O_6$ *in water.*
– – – – – – *Oxidation product* $C_{11}H_{10}O_6$ *in* 0·1N-NaOH.
× × × × *Deoxygladiolic acid in ethanol.*
. . . . . iso*Gladiolic acid in ethanol.*

by a carboxyl substituent (in *iso*gladiolic acid, Fig. 3) gives a different type of curve with a single peak at 298 mμ and an inflexion close to 250 mμ and a similar absorption curve (not reproduced) is given by the triacetyl derivative (III; R = OAc).

When the ultra-violet spectrum of a substance capable of showing keto–lactol tautomerism is examined for solutions in an excess of dilute sodium hydroxide, there is generally a displacement of the absorption maxima to longer wave-lengths compared with the absorption in acid solution or in a non-polar solvent, and this fact is frequently taken as indicative of the existence of the open-chain structure. Thus, Buu-Hoï and his co-workers successfully demonstrated the presence in solution of the open forms of *o*-formylbenzoic acid (Buu-Hoï and Lin-che-Kin, *Compt. rend.*, 1939, **209**, 221) and opianic acid (Buu-Hoï, *ibid.*, 1941, **212**, 242), and these findings were confirmed by examination of suitable model compounds of known structure. The success of this technique is dependent on the compounds' being stable in dilute sodium hydroxide solution. Even if decomposition takes place slowly (*e.g.*, benzil-2-carboxylic acid, Fig. 6), and particularly if decomposition is rapid and extensive in the time normally taken in obtaining the spectral data (*e.g.*,

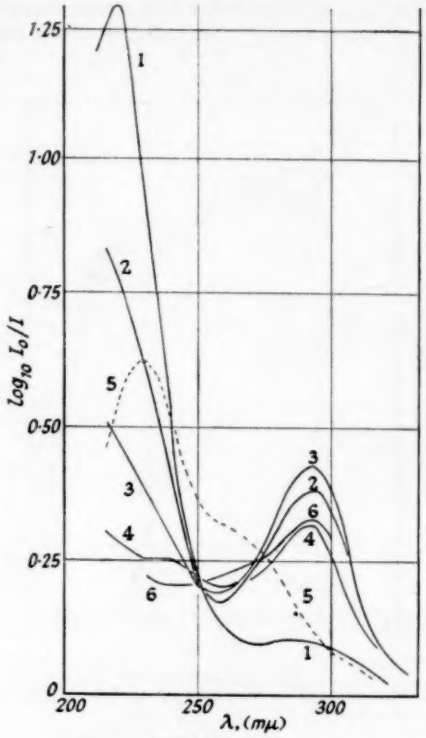
penicillic acid, Fig. 5), then erroneous conclusions may be drawn. Thus Shaw (*J. Amer. Chem. Soc.*, 1946, **68**, 2510), who obtained a curve similar to curve 4, Fig. 5, was led to conclude that penicillic acid exists in the keto-form in dilute sodium hydroxide whereas in fact it does not (Raphael, *J.*, 1947, 805; Ford *et al.*, *loc. cit.*): the peak at 295 mμ is due to a decomposition product (Ford *et al.*, *loc. cit.*). Acidification of the alkaline solution after 4 hours (curve 5, Fig. 5) does not restore the absorption curve to its original form (curve 1) and penicillic acid is not recovered on ether-extraction of the acidified solution.

FIG. 4.



Phthalaldehyde (1) *in* n-*hexane*, (2) *in* 0·1N-NaOH.

FIG. 5.



Penicillic acid;

1, *in* 0·1N-NaOH. l = 0·1 *cm.*
2, ,, *after* 1 *hour at* 26° ,,
3, ,, ,, 2 ,, ,,
4, ,, ,, 5 ,, ,,
5, 1 *ml. of soln.* (4) + 4 *ml. of* 0·1N-HCl, l = 1·0 *cm.*
6, *Soln.* (5) + 5 *ml. of* 0·1N-NaOH, ,,

The faintly yellow colour of a dilute alkaline solution of the colourless lactol form of benzil-2-carboxylic acid slowly deepens at room temperature (Fig. 6), but again this effect appears to be due to decomposition and not to the slow attainment of an equilibrium between the lactol and the keto ionic forms. The absorption spectrum of the yellow keto-form of benzil-2-carboxylic acid in dilute aqueous sodium hydroxide is identical with that of the lactol form in the same medium, the measurements being taken as quickly as possible after the solutions have been made up.

The gladiolic acid oxidation product, $C_{11}H_{10}O_6$ (IV), is stable to 0·1N-sodium hydroxide and behaves like the phthalaldehydic acids studied by Buu-Hoï and his co-workers (cf. bromo-opianic acid, Table 2). The absorption curve for its aqueous solution (Fig. 3) shows a

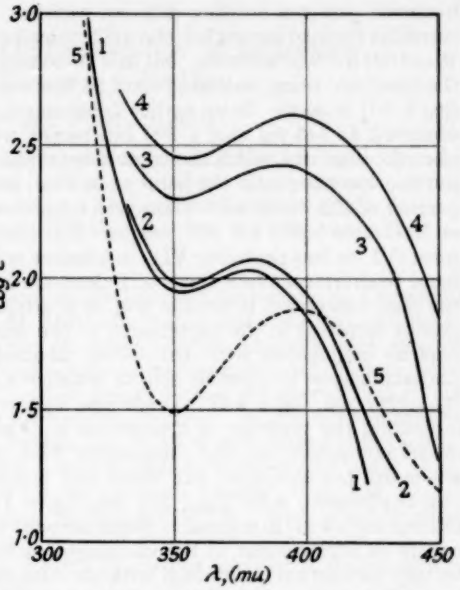


FIG. 6.

1, *Benzil-2-carboxylic acid (lactol or keto) in* 0·1N-NaOH.
2, *Benzil-2-carboxylic acid in* 0·1N-NaOH *after* 1 *day at* 20°.
3, *Benzil-2-carboxylic acid in* 0·1N-NaOH *after* 5 *days at* 20°.
4, *Benzil-2-carboxylic acid in* 0·1N-NaOH *after* 14 *days at* 20°.
5, *Benzil-2-carboxylic acid normal methyl ester.*

maximum at 296 mμ with an inflexion at 250 mμ; it is very similar to that of *iso*gladiolic acid (II; R = OH), and there is no doubt that the compound exists in the lactol form (IV*a*) in aqueous solution; but in 0·1N-sodium hydroxide the maxima are shifted to longer wave-lengths, demonstrating the presence of the open keto-form (IV*b*). Gladiolic acid,

TABLE 2. *Ultra-violet absorption data for gladiolic acid and its derivatives.*

Compound	Solvent	$\lambda_{max.}$	log ε
Deoxygladiolic acid (I*a*; R = H)	EtOH	306	3·62
		269	3·89
Acetylgladiolic acid (I*a*; R = OAc)	MeOH	306	3·48
		269	3·90
Methyl gladiolate (I*a*; R = OMe)	EtOH	305	3·50
		269	3·82
Ethyl gladiolate (I*a*; R = OEt)	EtOH	305	3·50
		269	3·91
*iso*Gladiolic acid (II; R = OH)	EtOH	298	3·72
		~245	3·93
Triacetylgladiolic acid hydrate (III; R = OAc)	EtOH	297	3·73
Oxidation product, $C_{11}H_{10}O_6$ (IV)	EtOH	300	3·40
		250	3·88
	H_2O	299	3·30
		~250	3·83
	0·1N-NaOH	310	3·40
		271	3·96
Bromo-opianic acid [a]	Aq. EtOH	312	3·5
		~250	3·5
	0·05N-NaOH	315	3·7
		280	4·1
Gladiolic acid	EtOH	305	3·48
		269	3·82
	H_2O	307	3·65
	(pH of soln., 3·9)	269	4·04
	0·1N-NaOH	276	3·08
Phthalaldehyde	*n*-Hexane	297	3·36
		255	3·95
	0·1N-NaOH	260 [b]	2·64 [b]
	McIlvaine buffer pH 2·97	261	2·88

[a] Buu-Hoï and Cagniant, *Compt. rend.*, 1941, **212**, 268. [b] Obtained within 30 mins. of the solution's being made up. Phthalaldehyde slowly undergoes decomposition in 0·1N-NaOH.

however, presents a rather different picture. The curves in water and in ethanol (Fig. 2) resemble those of deoxygladiolic acid, showing that gladiolic acid is in the lactol form (I*a*; R = OH) in these solvents; but in 0·1N-sodium hydroxide, in which gladiolic acid is stable, the spectrum being unaltered after 24 hours at 20°, only a weak absorption band at 276 mμ (log ε 3·1) is seen. In an earlier determination (Grove, *loc. cit.*), a second weak band was observed at 343 mμ (log ε 2·8) but recent work has shown that this band arose from a phenolic impurity which shows an intense absorption (log ε 4—4·5) in this region. Careful purification eliminates the band at 343 mμ, leaving only the weak band ot 276 mμ. Comparison of this curve with that given by phthalaldehyde in 0·1N-sodium hydroxide (Fig. 4) or McIlvaine buffer pH 2·97 suggests that gladiolic acid is in fact in a hydrated open-chain form (VI, or less probably VII) in alkaline solution. The shifting of the first absorption band to shorter wave-lengths with decrease in intensity in phthalaldehyde compared with the same compound in hexane (Fig. 4) is attributed to hydration involving both the formyl groups resulting in the suppression of the absorption pattern characteristic of a benzene nucleus conjugated with the C=O chromophore. Thus the absorption spectrum of phthalaldehyde in aqueous acid or alkaline solution (Table 2) is close to that of *o*-xylene ($\lambda_{max.}$ 262 mμ, log ε 2·47; Doub and Vandenbelt, *J. Amer. Chem. Soc.*, 1949, **71**, 2414), indicating the presence of a structure such as (VIII, R = R′ = H). Reliable data on a model compound strictly comparable with the gladiolic acid hydrate (VI) postulated above are not available, but Moser and Kohlenburg (*J.*, 1951, 804) have examined 2 : 6-dimethylbenzoic acid ($\lambda_{max.}$ 270 mμ, log ε 2·86) and 2 : 6-dimethoxybenzoic acid ($\lambda_{max.}$ 282 mμ, log ε 3·27) in ethanol. When account is taken of the small hypsochromic shift which occurs on replacement of the uncharged carboxyl substituent by the carboxyl ion, satisfactory correlation is obtained with the data for gladiolic acid. Thus the absorption spectrum of gladiolic acid in 0·1N-sodium hydroxide ($\lambda_{max.}$ 276 mμ, log ε 3·08) corresponds more closely with that of a 2 : 6-disubstituted benzoic acid than with that of a substituted phthalide [cf. triacetylgladiolic acid hydrate (III; R = OAc) ($\lambda_{max.}$ 297 mμ, log ε 3·73)]; and gladiolic acid is considered to be a hydrated keto-form (VI or VII), rather than a hydrated lactol form, in this medium. Of the two possible structures, (VI) is the more probable since the hydration phenomenon is only observed in the gladiolic acid anion where two formyl groups are present; there is no spectroscopic evidence for the hydration in aqueous solution of the single formyl substituent present in the lactol form (I*a*).

It may be concluded that whereas gladiolic acid is present in the lactol form in the solid state, an equilibrium between the lactol and the open-chain form exists in aqueous solution, pH being the determining factor. Similar conclusions apply to the oxidation product $C_{11}H_{10}O_6$. The esters of gladiolic acid described by Grove (*loc. cit.*) are shown conclusively to be *pseudo*-esters and the significance of this conclusion in the general problem of the correlation of chemical structure and biological activity in the gladiolic acid series of compounds will be discussed elsewhere.

I thank Dr. B. W. Bradford, Imperial Chemical Industries Limited, Billingham Division, and Mr. H. A. Willis, Imperial Chemical Industries Limited, Plastics Division, for ultra-violet and infra-red facilities, and Mrs. J. Zealley for assistance in the preparation of gladiolic acid hemihydrate.

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The Frythe, Welwyn, Herts. [*Received, April 29th*, 1952].

645. *The Low-temperature Polymerisation of* iso*Butene. Part III.* The End-group Problem.*

By M. St. C. Flett and P. H. Plesch.

Poly*iso*butenes were prepared in hexane solution by using titanium tetrachloride as catalyst and trichloroacetic acid as co-catalyst. The polymers were examined by infra-red spectroscopy. The predominant end-group was the methylene group. Trisubstituted double bonds and trichloroacetate end-groups were also found.

The first observations on the infra-red spectrum of poly*iso*butene were made by Thompson and Torkington (*Trans. Faraday Soc.*, 1945, **41**, 246), who stated that the main features of the spectrum were independent of the degree of polymerisation for molecular weights between 10^3 and 10^5. As the theory of cationic polymerisation developed, it became of interest to examine poly*iso*butenes of low molecular weight for the presence of end-groups which might shed some light on the reaction mechanisms involved. The first investigation of this nature (Dainton and Sutherland, *J. Polymer Sci.*, 1949, **4**, 37) showed that poly*iso*butene of low molecular weight, prepared with boron fluoride as catalyst and water as co-catalyst by the method of A. G. Evans and his collaborators (*Nature*, 1946, **158**, 94; *J. Polymer Sci.*, 1949, **4**, 359), had as end-groups mainly $R^1R^2C{:}CH_2$, with possibly small quantities of $R^1R^2C{:}CHR^3$ and —OH groups.

The present work is concerned with the spectra of various samples of poly*iso*butene prepared with titanium tetrachloride as catalyst.

Experimental

Hexane, *iso*butene, and titanium tetrachloride were purified as described previously.* A number of different co-catalysts were used, and polymers were prepared by two different methods: (1) The adiabatic technique described previously (Plesch, *loc. cit.*). (2) An isothermal method at 0°, in which the reaction was followed by observing the change in the vapour pressure of the polymerising solution.

Method (1) with initial temperatures of −20° to −50° gave polymers of mean molecular weight $2—3 \times 10^4$, and method (2) gave molecular weights of about 500—1000. The spectra of two polymers of molecular weight 5×10^5, prepared, respectively, with water and trichloroacetic acid as co-catalysts, were used for comparison.

In method (2) hexane and *iso*butene were distilled into the evacuated reaction vessel fitted with a phial breaker, and the titanium tetrachloride and co-catalysts were introduced by crushing weighed, sealed phials. The batch-size was about 100 c.c., the concentration of *iso*butene about 30% wt./wt., and the concentrations of catalyst and co-catalyst of the order of 100 and 10 millimole/l., respectively. In the earlier experiments, after the end of the reaction, about 5 c.c. of alcohol were added to the reaction mixtures, whereby the titanium tetrachloride was precipitated, as a heavy, greenish, transparent layer. The polymer solutions were separated from this and then either washed with dilute sodium hydrogen carbonate and water and then dried, or they were twice precipitated by alcohol and redissolved in hexane. These specimens were not prepared originally for infra-red analysis, and it transpired in the course of this work that the use of alcohol to precipitate the titanium tetrachloride gave rise to certain artefacts which will be discussed below. Specimen 305 is typical of the products obtained by this procedure. The polymers in the preparation of which water or sulphuric acid were used as co-catalysts were also separated from the reaction mixture by this method.

Subsequently, in order to avoid the artefacts, poly*iso*butenes prepared by method (2) at 0° with trichloroacetic acid as co-catalyst were precipitated by acetone, then redissolved in hexane and dried. Specimen 318 is typical of these products.

The spectra were measured with a Hilger D. 209 infra-red spectrometer, single-beam photographic recording being used. Between 600 and 1400 cm.$^{-1}$, films about 0·1 mm. thick proved

* Part II, *J.*, 1950, 543.

convenient, and at shorter wave-lengths films of 0·5 mm. thickness were used. The wave-numbers recorded are believed to be accurate to at least ± 2 cm.$^{-1}$.

Molecular weights were determined viscometrically as described previously (Plesch, *loc. cit.*) or cryoscopically in *cyclo*hexane.

Methyl, ethyl, and *tert.*-butyl trichloroacetates were commercial products which were purified by standard methods. Their infra-red spectra were recorded for comparison.

Results.—The conclusions set out below were obtained by examining the spectra of some two dozen poly*iso*butenes prepared and treated in different ways. Most of the results were obtained from the spectra of polymers produced by method (2). The mean molecular weights of the polymers made by method (1) were too high for there to be sufficient end-groups to give conclusive spectra; but those bands which were found to differentiate the spectra of these polymers from those of the very high polymers, *i.e.*, the end-group bands, corresponded closely with the end-group bands found in the low polymers.

Unsaturated End-groups.—If the polymer contained terminal double bonds, these could be expected to give rise to bands characteristic of hydrocarbons such as 2 : 4 : 4-trimethylpent-1- and -2-ene, and therefore the infra-red absorption spectra of these two hydrocarbons were used for comparison.

It was found that the presence of $R^1R^2C{:}CH_2$ groups was indicated in all polymers of molecular weight less than about 3×10^4 [whether prepared by method (1) or (2)] by the presence of well-marked bands at 895, 1642, and 1780 cm.$^{-1}$. If trichloroacetic acid had been used as co-catalyst the spectra showed a strong carbonyl band near 1775 cm.$^{-1}$, which could be distinguished from the double-bond band in this vicinity by the fact that its intensity was greater than that of the band at 1642 cm.$^{-1}$, whereas the double-bond band at 1780 cm.$^{-1}$ is much weaker than that at 1642 cm.$^{-1}$. The assignment of these bands is confirmed by the spectra of polymers treated with bromine water, which had shown these bands originally. This treatment causes the almost complete disappearance of the bands at 895 and 1780 cm.$^{-1}$, and a reduction in the intensity of the band near 1650 cm.$^{-1}$.

The partial persistence of a band near 1650 cm.$^{-1}$ after the bromination is ascribed to its being due partly to double bonds of the type $R^1R^2C{:}CHR_3$, which are much more difficult to brominate. This assignment is confirmed by the presence of a band at 825 cm.$^{-1}$, which is characteristic of trisubstituted double bonds. Bands near those frequencies are found in the spectra of polymers made with water, sulphuric acid, and trichloroacetic acid as co-catalysts, but the intensity of the bands compared to that of the $R^1R^2C{:}CH_2$ band at 895 cm.$^{-1}$, after allowance for the difference in extinction coefficient, indicates that the latter group is present in much higher concentration.

The spectra of poly*iso*butenes prepared by method (2) with water or sulphuric acid as co-catalyst were very similar. In addition to the usual methylene bands, the former showed bands at 803, 1019, and 1102 cm.$^{-1}$, and the latter showed strong bands at 800, 828, 1019, 1075, and 1102 cm.$^{-1}$. Evacuation of the latter specimen at 80° for several hours removed the bands at 828 and 1102 cm.$^{-1}$, the 1075 band became very prominent, and new bands appeared at 1117, 1267, and 1286 cm.$^{-1}$. The interpretation of these changes is not clear; the bands near 800 cm.$^{-1}$ are, as before, assigned to trisubstituted double bonds.

The Trichloroacetate End-group.—According to a recent suggestion (Plesch, *loc. cit.*), one of the ways in which the growth of poly*iso*butene chains, catalysed by titanium tetrachloride and trichloroacetic acid, may come to an end, is by formation of a terminal trichloroacetate group from the ion-pair at the growing end of the polymer chain. It was an obvious step to search for this group by infra-red spectroscopy, but this has proved unexpectedly difficult. The principal reason for this was the production of a number of artefacts; by use of acetone instead of alcohol these artefacts were eliminated.

The bands due to esters of trichloroacetic acid present in the polymer were identified as those which vanished when a solution of the polymer was refluxed with an aqueous solution of sodium hydroxide.

The table gives the absorption bands of methyl, ethyl, and *tert.*-butyl trichloroacetates in the region 670—1100 cm.$^{-1}$. It also shows the absorption bands in the spectra of specimens 305 and 318 which disappeared when these polymers were treated with alkali. In addition, the strong carbonyl band near 1760 cm.$^{-1}$, present in the spectra of both polymers, vanished on hydrolysis.

The table shows that No. 305 contained methyl and ethyl trichloroacetate, presumably derived from the precipitant. No. 318 contained neither of these, but its spectrum shows other bands which are now attributed to trichloroacetate end-groups, *i.e.*, poly(*iso*butyl trichloro-

acetate). This diagnosis was confirmed by hydrolysing some of polymer No. 318 with dilute sodium hydroxide: on acidification the aqueous layer there was a marked smell of trichloroacetic acid. The acid solution was thoroughly extracted with hexane and the infra-red spectrum of the hexane then showed the presence of trichloroacetic acid.

The Chlorine Content.—Micro-analysis of poly*iso*butenes of molecular weights of 500—10,000 showed not only that those prepared with trichloroacetic acid contained chlorine, but that even when water or sulphuric acid was used as co-catalyst chlorine was present. (In polymers prepared with the latter co-catalyst a trace of sulphur was also found.) However, for polymers of the same molecular weight the chlorine content is much smaller than in the polymers prepared with trichloroacetic acid.

Main absorption bands of methyl, ethyl, and tert.*-butyl trichloroacetates, and the absorption bands removed by treatment with alkali in the spectra of poly*iso*butenes* 305 *and* 318, *in the region* 650—1100 *cm.*$^{-1}$.

Me	Et	Bu^t	No. 305	No. 318	Me	Et	Bu^t	No. 305	No. 318
683	683	683	683	(683)	—	—	—	—	844
—	—	—	727	727	—	—	870	—	—
—	750	—	750	—	—	885 *	—	—	—
(758)	—	—	—	—	916 *	—	—	—	—
—	—	785	—	—	—	—	968	—	—
—	—	—	—	812	1018	—	—	1018	—
—	828	826	826	—	—	1030	—	(1030)	—
835	—	—	831	—	—	—	(1037)	—	—

1. The parentheses indicate that the bands are weak.
2. The asterisks indicate bands which cannot be detected in the polymer spectra because of their proximity to polymer bands.

The presence in the polymer of chlorine, which must have come from the catalyst, indicates a new and hitherto unsuspected feature of these polymerisations. It may well be due to the reaction of titanium tetrachloride or hydrochloric acid with terminal double bonds in the polymer. It is noteworthy that when poly*iso*butene is kept in contact with titanium tetrachloride for some weeks a violet colour, characteristic of titanium dichloride develops.

The presence of chlorine in all the poly*iso*butenes prepared with titanium tetrachloride is in apparent contradiction to an earlier statement (Plesch, *loc. cit.*, Table III). The explanation lies in the higher molecular weights of the specimens used in the earlier work. Subsequent tests of these specimens (Nos. 119 and 121) by the Beilstein flame test showed that they too contained traces of chlorine.

In agreement with the analytical results, the spectra of all the polymers concerned show the C–Cl band at 683 cm.$^{-1}$, though often it is only vestigial.

Discussion.—The poly*iso*butene chain is now believed to be propagated by a carbonium ion associated with an anion consisting of a complex between catalyst and co-catalyst, less one proton. The termination can take place by several different mechanisms which have been discussed by a number of authors (Hamann, *Angew. Chem.*, 1951, **63**, 231; for older literature see Plesch, *J. Appl. Chem.*, 1951, 269). One alternative is the loss of a proton from carbon atom 1, one of the methyl groups attached to the positive carbon atom at the growing end of the chain, leaving the polymer with a terminal $R^1R^2C{:}CH_2$ group. Since this is undoubtedly the predominant end-group in all the polymers examined, this seems to be the most probable process. The $R^1R^2C{:}CHR^3$ groups could be formed in a similar way by loss of a proton from carbon atom 3, or they may be formed by isomerisation of the $C{:}CH_2$ groups under the influence of the catalytic complex.

It is frequently found that polymerisations under the conditions described above may cease before all the monomer has been consumed, and that they can be restarted by the addition of more trichloroacetic acid (Plesch, *loc. cit.*). If this is accepted as evidence that the acid as such is consumed during the reaction, the most likely explanation may be that the ion-pair at the growing end of the polymer chain rearranges to form poly(*iso*butyl trichloroacetate). The evidence presented here strongly supports this.

The nature of the end-groups formed when the trichloroacetate group is removed by hydrolysis, or when water or sulphuric acid is used as co-catalyst, is less clear. The pre-

dominant end-groups are undoubtedly double bonds, but there are certainly other end-groups as well. In view of the uncertain band assignments involved, the matter is not now discussed further.

This work was carried out at Manchester University and at the Blackley Laboratories of Imperial Chemical Industries Limited.

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646. *New Syntheses of Heterocyclic Compounds. Part XVII.* Diethylaminoethyl* 1 : 3-*Dimethyl-2-aza-9-fluorylideneacetate.*

By B. N. FEITELSON and V. PETROW.

Two routes to 1 : 3-dimethyl-2-aza-9-fluorylideneacetic acid (IV; R = H) have been investigated. (i) Reaction of 1 : 3-dimethyl-2-azafluorenone (I) with acetylene gave 9-ethynyl-1 : 3-dimethyl-2-azafluorenol (II; R = H), which is partially reduced to 1 : 3-dimethyl-9-vinyl-2-azafluorenol (III), from which 1 : 3-dimethyl-2-aza-9-fluorylidene-ethanol (V; R = H) was obtained by anionotropic rearrangement. Its oxidation to (IV; R = H) could not, however, be effected. (ii) Condensation of (I) with ethoxyacetylene gave 9-ethoxyethynyl-1 : 3-dimethyl-2-azafluorenol (II; R = OEt), from which the desired acid (IV; R = H) was obtained by anionotropic rearrangement.

The acid (IV; R = H) was converted into the diethylaminoethyl ester, which was required for biological study.

ATTEMPTS to prepare 1 : 3-dimethyl-2-azafluorene-9-carboxylic acid for conversion into the diethylaminoethyl ester, reported in Part XIV (Feitelson and Petrow, *J.*, 1952, 228), proved unsuccessful owing to the inherent instability of the acid (cf. also Fox, Lewis, and Wenner, *J. Org. Chem.*, 1951, **16**, 1259). We therefore turned our attention to the synthesis of the corresponding analogue (IV; R = H), hoping thereby to obtain a substance less liable to undergo decarboxylation.

First, 1 : 3-dimethyl-2-azafluorenone (I) was condensed with acetylene in the presence of potassium *tert.*-butoxide (cf. Nef, *Annalen*, 1899, **308**, 264) to give 9-ethynyl-1 : 3-dimethyl-2-azafluorenol (II; R = H) in excellent yield. The structure assigned to this compound was confirmed by (i) oxidation to 1 : 3-dimethyl-2-azafluorenone (I) (see below), (ii) formation of an unstable silver salt which deflagrated violently when heated, (iii) formation of a blue colour with concentrated sulphuric acid, and (iv) hydrogenation in presence of palladium–calcium carbonate to 1 : 3-dimethyl-9-vinyl-2-azafluorenol (III) and 9-ethyl-1 : 3-dimethyl-2-azafluorenol.

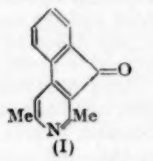
Anionotropic rearrangement of (III) into the alcohol (V; R = H) could not be effected by means of trichloroacetic acid (Dimroth, *Ber.*, 1938, **71**, 1336). The change proceeded smoothly, however, when (III) was treated with phosphorus tribromide in chloroform (Karrer and Helfenstein, *Helv. Chim. Acta*, 1931, **14**, 78; Ruzicka and Müller, *ibid.*, 1939, **22**, 416). Reaction of the bromo-compound so formed with anhydrous potassium acetate in acetic acid led to 1 : 3-dimethyl-2-aza-9-fluorylidene-ethyl acetate (V; R = Ac), from which 1 : 3-dimethyl-2-aza-9-fluorylidene-ethanol (V; R = H) was obtained by hydrolysis. Attempts to convert this compound into the desired acid (IV; R = H) by oxidation, however, proved uniformly unsuccessful, 1 : 3-dimethyl-2-azafluorenone (I) being invariably obtained.

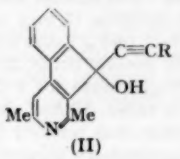
Inter alia, we examined the conversion of (II; R = H) into the acetylenic carboxylic acid (II; R = CO_2H) employing the procedure of Theobald and Adams (*J. Amer. Chem.*

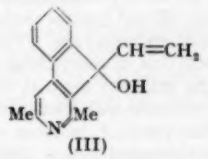
* Part XVI, *J.*, 1952, 784.

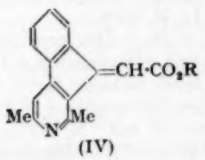
Soc., 1943, **65**, 2208; see also Haynes and Jones, *J.*, 1946, 503, 954) whereby carboxylation of the corresponding Grignard reagent is effected under pressure. An unexpected difficulty was here encountered in that, although (II; R = H) passed smoothly into the Grignard reagent, the latter proved to be completely insoluble in benzene, which is the solvent of choice in this instance. Attempts to carboxylate the reaction mixture by contact with solid carbon dioxide in an autoclave for 24 hours thus proved unsuccessful, the bulk of the starting material being recovered unchanged after hydrolysis. Similar results have been reported by Haynes and Jones (*loc. cit.*).

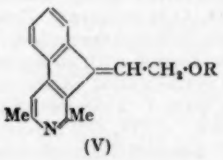
Attempts to convert 9-ethynyl-1 : 3-dimethyl-2-azafluorenol (II; R = H) into the corresponding hydroxy-acid by oxidation likewise proved discouraging. Ozone, which is claimed to be satisfactory for this purpose (Hurd and Christ, *J. Org. Chem.*, 1936, **1**, 141) failed to give the hydroxy-acid when passed through a solution of the acetylenic alcohol in acetic acid, the bulk of the starting product being recovered unchanged. Neutral


(I)


(II)


(III)


(IV)


(V)

potassium permanganate in acetone (Nazarov and Kuznetsova, *Chem. Abs.*, 1942, **36**, 1296) gave 1 : 3-dimethyl-2-azafluorenone, presumably by way of the required acid, which thus resembles 1 : 3-dimethyl-2-azafluorenone-9-carboxylic acid in the facility with which it undergoes decarboxylation.

9-Ethoxyethynyl-1 : 3-dimethyl-2-azafluorenol (II; R = OEt) was readily obtained in excellent yield from 1 : 3-dimethyl-2-azafluorenone (I) and ethoxyethynylmagnesium bromide (Arens and van Dorp, *Nature*, 1947, **160**, 189) and was smoothly rearranged by dilute sulphuric acid in a few minutes at 100° (cf. Heilbron, Jones, Julia, and Weedon, *J.*, 1949, 1823); ethyl 1 : 3-dimethyl-2-aza-9-fluorylideneacetate (IV; R = Et) was thus obtained in 45% yield. Hydrolysis with aqueous-ethanolic potassium carbonate furnished the corresponding acid (IV; R = H), from which the diethylaminoethyl ester (IV; R = $CH_2 \cdot CH_2 \cdot NEt_2$), the required analogue of the antispasmodic drug Trasentin, was obtained *via* the acid chloride.

Experimental

M. p.s are uncorrected. Microanalyses are by Drs. Weiler and Strauss, Oxford.

9-*Ethynyl*-1 : 3-*dimethyl*-2-*azafluorenol* (II; R = H).—Potassium (18 g.) was dissolved in *tert.*-amyl alcohol (350 ml.) in a current of dry nitrogen. The solution was diluted with dry ether (350 ml.) and saturated with acetylene which had been passed through concentrated sulphuric acid. 1 : 3-Dimethyl-2-azafluorenone (10·45 g.) in warm benzene (150 ml.) was then added fairly rapidly with stirring, passage of acetylene being maintained for a further 4 hours. After decomposition with saturated aqueous ammonium chloride, the ethereal layer was removed and shaken repeatedly with ammonium chloride solution, then with water, after which it was extracted with dilute hydrochloric acid. The resulting hydrochloride formed a sludge which was collected and cautiously decomposed with potassium hydroxide solution, to give **9-*ethynyl*-1 : 3-*dimethyl*-2-*azafluorenol*** (96%) in small needles, m. p. 210—211° (Found : C, 81·2; H, 5·5; N, 6·0. $C_{14}H_{13}ON$ requires C, 81·7; H, 5·5; N, 6·0%) after crystallisation from benzene.

9-*Ethyl*-1 : 3-*dimethyl*-2-*azafluorenol*.—The foregoing alcohol (2·35 g.) in absolute ethanol

(50 ml.) was shaken with hydrogen in the presence of 2% palladium–calcium carbonate (1 g.) until absorption was complete. Crystallisation of the product from benzene gave *9-ethyl-1 : 3-dimethyl-2-azafluorenol* (85%), glistening flakes, m. p. 169—170° (Found: C, 80·1; H, 7·1; N, 6·1. $C_{16}H_{17}ON$ requires C, 80·3; H, 7·1; N, 5·9%). The *picrate*, after crystallisation from ethanol, formed yellow needles, m. p. 204—205° (Found: C, 56·3; H, 4·2; H, 12·0. $C_{16}H_{17}ON,C_6H_3O_7N_3$ requires C, 56·4; H, 4·3; N, 12·0%).

1 : 3-Dimethyl-9-vinyl-2-azafluorenol (III).—9-Ethynyl-1 : 3-dimethyl-2-azafluorenol (2·35 g.) in absolute ethanol (50 ml.) was shaken with hydrogen in the presence of palladium–calcium carbonate (0·25 g.; 2%) until 1 mol. of hydrogen had been absorbed. The product, after crystallisation from benzene–light petroleum, yielded *1 : 3-dimethyl-9-vinyl-2-azafluorenol*, fluffy needles, m. p. 165° (Found: C, 80·6; H, 6·4; N, 6·0. $C_{16}H_{15}ON$ requires C, 81·0; H, 6·3; N, 5·9%). The *picrate* separated in fine yellow needles, m. p. 199—200° (Found: C, 56·1; H, 3·9; N, 11·8. $C_{16}H_{15}ON,C_6H_3O_7N_3$ requires C, 56·7; H, 3·9; N, 12·0%), from ethanol.

1 : 3-Dimethyl-2-aza-9-fluorylidene-ethyl Acetate (V; R = Ac).—1 : 3-Dimethyl-9-vinyl-2-azafluorenol (3·8 g.) in dry chloroform (27 ml.) was treated with phosphorus tribromide (3·0 g.) in dry chloroform (27 ml.), after which dry pyridine (3 ml.) was added and the mixture kept for 2 hours at room temperature. The product (5·3 g.) was collected and dissolved in acetic acid (100 ml.), a solution of anhydrous sodium acetate (from 25 g. crystals) in acetic acid (100 ml.) added, and the mixture kept at room temperature for 2 days. After filtration from sodium bromide, the solution was concentrated *in vacuo*, diluted with water, and basified with aqueous ammonia. The product, isolated with ether, was purified from benzene, to give *1 : 3-dimethyl-2-aza-9-fluorylideneethyl acetate* (30%), long feathery needles, m. p. 165—166° (Found: C, 77·5; H, 5·9; N, 5·0. $C_{18}H_{17}O_2N$ requires C, 77·4; H, 6·1; N, 5·0%).

1 : 3-Dimethyl-2-aza-9-fluorylidene-ethanol (V; R = H).—The foregoing compound (1·15 g.) in alcohol (25 ml.) was treated with an aqueous solution of potassium carbonate (1·15 g.) under reflux for 1 hour. Crystallisation of the product from benzene–light petroleum, and subsequently from benzene, gave *1 : 3-dimethyl-2-aza-9-fluorylidene-ethanol* (80%), m. p. 178° (Found: C, 81·2; N, 6·1; N, 5·6. $C_{16}H_{15}ON$ requires C, 81·0; H, 6·3; N, 5·9%).

9-Ethoxyethynyl-1 : 3-dimethyl-2-azafluorenol (II; R = OEt).—Ethoxyacetylene (5 g.) (Jacob, Cramer, and Hanson, *J. Amer. Chem. Soc.*, 1942, **64**, 223; Van Dorp, Arens, and Stephenson, *Rec. Trav. chim.*, 1951, **70**, 289) in dry ether (15 ml.) was added with vigorous stirring to ethereal ethylmagnesium bromide (from 1·7 g. of magnesium) and ethyl bromide (8·0 g.) kept at 0°. The mixture was allowed to warm to room temperature and then heated under gentle reflux for 15 minutes, forming two layers. It was cooled to 0° and a solution of 1 : 3-dimethyl-2-azafluorenone (5 g.) in dry benzene (100 ml.) added fairly rapidly with vigorous stirring. After being allowed to warm to room temperature, the mixture was gently refluxed for 30 minutes, cooled, and decomposed with ice-cold saturated ammonium chloride solution. Crystallisation of the product from benzene gave *9-ethoxyethynyl-1 : 3-dimethyl-2-azafluorenol* (64%), prisms, m. p. 125—126° (Found: C, 77·0; H, 6·0; N, 4·8. $C_{18}H_{17}O_2N$ requires C, 77·5; H, 6·1; N, 5·0%).

Ethyl 1 : 3-Dimethyl-2-aza-9-fluorylideneacetate (IV; R = Et).—The foregoing compound (2·0 g.) was added to sulphuric acid (20 ml. of 10%), and the resulting solution warmed for 5—10 minutes on the water-bath. The product, isolated with ether, was purified from ether–light petroleum, to give *ethyl 1 : 3-dimethyl-2-aza-9-fluorylideneacetate*, long needles, m. p. 90—92° (Found: C, 77·9; H, 5·8; N, 4·8. $C_{18}H_{17}O_2N$ requires C, 77·5; H, 6·1; N, 5·0%).

1 : 3-Dimethyl-2-aza-9-fluorylideneacetic Acid (IV; R = H).—The foregoing compound (1·3 g.) in methanol (10 ml.), and a solution of potassium carbonate (1·3 g.) in water (5 ml.), were heated under reflux for 30 minutes. Dilution with water led to precipitation of some (I), which was removed by filtration. After removal of methanol under reduced pressure, the aqueous alkaline liquors were neutralised with 2N-sulphuric acid, and the precipitated solids collected and crystallised from methanol. *1 : 3-Dimethyl-2-aza-9-fluorylideneacetic acid monohydrate* (36%) had m. p. 267—268° (Found: C, 71·0; H, 5·1; N 5·2. $C_{16}H_{13}O_2N,H_2O$ requires C 71·4; H 5·6; N 5·2%).

2-Diethylaminoethyl 1 : 3-Dimethyl-2-aza-9-fluorylideneacetate (IV; R = $CH_2{\cdot}CH_2{\cdot}NEt_2$).—The foregoing acid (1·0 g.), benzene (10 ml.), and excess of thionyl chloride were heated on the water-bath for 45 minutes. After filtration, excess of thionyl chloride was removed under reduced pressure, and the residue heated with 2-diethylaminoethanol (2 mols.) in benzene under reflux for 2 hours. After basification, the product, in ethanol, was treated with dry hydrogen chloride, and the precipitated solids collected and crystallised from chloroform–ethanol. *2-Diethylaminoethyl 1 : 3-dimethyl-2-aza-9-fluorylideneacetate dihydrochloride sesquihydrate* (36%)

formed pale yellow prismatic needles, m. p. 215° (decomp.) (Found: C 58·5; H 6·8; N 6·7; Cl, 16·0. $C_{22}H_{36}O_2N_2,2HCl,1\frac{1}{2}H_2O$ requires C, 58·7; H, 6·9; N, 6·2; Cl, 15·8%). The *dipicrate* of the base formed large needles, m. p. 202—203° (Found: C, 50·2; H, 3·7; N, 13·8. $C_{22}H_{36}O_2N_2,2C_6H_3O_7N_3$ requires C, 50·5; H, 4·0; N, 13·9%).

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CHEMICAL RESEARCH LABORATORIES,
THE BRITISH DRUG HOUSES, LTD., LONDON, N.1. [*Received, May 16th*, 1952].

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647. *Steroids and Walden Inversion. Part VII.* The Stereochemistry and the Mechanism of the* i-*Steroid Rearrangement.*

By C. W. SHOPPEE and G. H. R. SUMMERS.

The *i*-steroid rearrangement is shown to involve inversion of configuration at $C_{(3)}$ and to yield 6β-substituted derivatives of 3 : 5-*cyclo*steroids. A 6α-substituted 3 : 5-*cyclo*steroid has been prepared indirectly. The rearrangement exhibits some analogies with Wagner substitution and a mechanism for the change is suggested and discussed.

THE *i*-steroid rearrangement is a general reaction whereby derivatives of 3β-hydroxy-Δ^5-steroids afford 6-substituted 3 : 5-*cyclo*steroids. Thus methanolysis of cholesteryl toluene-*p*-sulphonate or chloride gives cholesteryl methyl ether, m. p. 84°, $[\alpha]_D$ −46°, but in the presence of potassium acetate furnishes *i*-cholestanyl methyl ether (6-methoxy-3 : 5-*cyclo*cholestane), m. p. 79°, $[\alpha]_D$ +55° (Stoll, *Z. physiol. Chem.*, 1932, **207**, 147; Wagner-Jauregg and Werner, *ibid.*, 1932, **213**, 119). These observations were, some four years later, the subject of intensive investigation by Heilbron and his collaborators in this country and by Wallis and his co-workers in America; both schools at one time or another regarded the "abnormal" methyl ether as *epi*cholesteryl methyl ether (Heilbron, Beynon, and Spring, *J.*, 1936, 907; 1937, 406; Wallis, Fernholz, and Gephart, *J. Amer. Chem. Soc.*, 1937, **59**, 137). This interim conclusion, which had been criticised by Ruzicka, Goldberg, and Bosshard (*Helv. Chim. Acta*, 1937, **20**, 541), was shown to be incorrect by the preparation of genuine *epi*cholesteryl methyl ether, m. p. 88—89°,† $[\alpha]_D$ −46° (Wallis and Ford, *J. Amer. Chem. Soc.*, 1937, **59**, 1415). Lack of olefinic unsaturation in the "abnormal" ether, the related acetate, and the parent alcohol was explained by Wallis in terms of the 3 : 5-*cyclo*steroid formulation, which he suggested by analogy with the transformation of sabinene hydrate into terpinen-4-ol. The formula requires the presence of a secondary hydroxyl group at $C_{(6)}$, which was proved by oxidation of the alcohol to a ketone *i*-cholestanone (Ford, Chakravorty, and Wallis, *J. Amer. Chem. Soc.*, 1938, **60**, 413) recognised by Heilbron as 3 : 5-*cyclo*cholestan-6-one and hydrogenated to give cholestan-6-one (Heilbron, Hodges, and Spring, *J.*, 1938, 759). Similarly 3 : 5-*cyclo*androstane-6 : 17-dione was converted into 3′ : 3′ : 9-trimethyl*cyclo*pentanophenanthrene to prove the presence of an oxygen atom at $C_{(6)}$ (Butenandt and Suranyi, *Ber.*, 1942, **75**, 597).

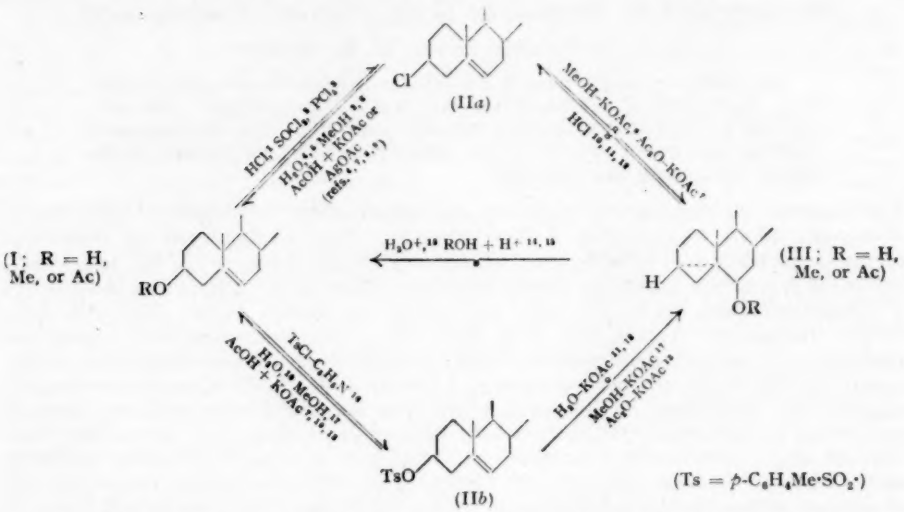
Further chemical and physical evidence for the presence of a 3-membered ring in 3 : 5-*cyclo*steroids has recently been given by the conversion of 3 : 5-cholestane with hydrogen chloride–acetic acid into A-norcholest-3(5)-ene (Schmid and Kägi, *Helv. Chim. Acta*, 1950, **33**, 1582), the partial synthesis of which we have recently achieved (Shoppee and Summers, *J.*, 1952, 2528). Indirect evidence is provided by simple aliphatic analogues of the *i*-steroid change; thus 4-methylpent-3-enyl chloride is hydrolysed by water to dimethyl*cyclo*propylcarbinol which is reconverted by hydrochloric acid into 4-methylpent-3-enyl chloride (Bruylants and Dewael, *Bull. Sci. Acad. Roy., Belg.*, 1928, [v], **14**, 140; Favorskaya and Fridman, *J. Gen. Chem. U.S.S.R.*, 1945, **15**, 421); *cyclo*propylcarbinol with phosphorus tribromide gives a bromide converted by the action of magnesium followed by carbon dioxide into allylacetic acid (L. I. Smith and McKenzie, *J. Org. Chem.*, 1950,

* Part VI, *J.*, 1950, 687.
† We have observed a double m. p. 82—84° with resolidification and remelting at 88—89°.

15, 74); and chlorination of methyl*cyclo*propane gives a mixture containing approximately equal quantities of *cyclo*propylmethyl chloride and but-3-enyl chloride (Roberts and Mazur, *J. Amer. Chem. Soc.*, 1951, **73**, 2509).

The infra-red absorption spectra of 3 : 5-*cyclo*cholestane (Barton, *J.*, 1951, 1444) and of various 6-methoxy-3 : 5-*cyclo*steroids (Josien, Fuson, and Cary, *J. Amer. Chem. Soc.*, 1951, **73**, 4445) show bands in the region 1010—1020 and at 890 cm.$^{-1}$, which have been tentatively identified with deformation of the *cyclo*propane ring and with the band at 1000—1020 cm.$^{-1}$ reported for alkyl-substituted *cyclo*propane derivatives by Derfer, Pickett, and Boord (*ibid.*, 1949, **71**, 1482).

The principal experimental facts concerning the *i*-steroid rearrangement relate to the cholestane series, and may be summarised as follows :

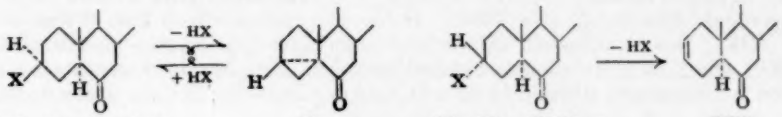


[1] Shoppee and Summers, *J.*, 1952, 1786. [2] Diels, Abderhalden, and Blumberg, *Ber.*, 1904, **37**, 3092; 1911, **44**, 2847. [3] Mauthner, *Monatsh.*, 1894, **15**, 87. [4] *Idem*, *ibid.*, p. 362. [5] Marker, *J. Amer. Chem. Soc.*, 1935, **57**, 1755. [6] Wagner-Jauregg and Werner, *Z. physiol. Chem.*, 1932, **213**, 119. [7] Shoppee and Summers, this paper. [8] Bergmann, *J. Amer. Chem. Soc.*, 1938, **60**, 1996. [9] Shoppee, *J.*, 1946, 1147. [10] Heilbron, Beynon, and Spring, *J.*, 1936, 907. [11] *Idem*, *J.*, 1937, 1459. [12] Wallis and Ford, *J. Amer. Chem. Soc.*, 1937, **59**, 1415. [13] Wallis, Fernholz, and Gephart, *ibid.*, p. 137. [14] McKennis, *ibid.*, 1947, **69**, 2565; 1948, **70**, 675. [15] Winstein and Schlesinger, *ibid.*, 1948, **70**, 3528. [16] Freudenberg and Hess, *Annalen*, 1926, **448**, 121. [17] Stoll, *Z. physiol. Chem.*, 1932, **207**, 147. [18] Hafez, Halsey, and Wallis, *Science*, 1949, **110**, 474.

The reaction (I ⟶ II) proceeds with complete retention of configuration at $C_{(3)}$. A complete proof of the β-configuration at $C_{(3)}$ of cholesterol (I; R = H) has been given (Shoppee, *J.*, 1948, 1032). The structure of cholesteryl chloride (II*a*), suggested by that of cholesteryl iodide (Carlisle and Crowfoot, *Proc. Roy. Soc.*, 1945, *A*, **184**, 64), is established by the proof that its 5 : 6-dihydro-derivative is 3β-chlorocholestane (Shoppee, *J.*, 1946, 1138, 1147); the structure of the toluene-*p*-sulphonate (II*b*) follows from that of cholesterol.

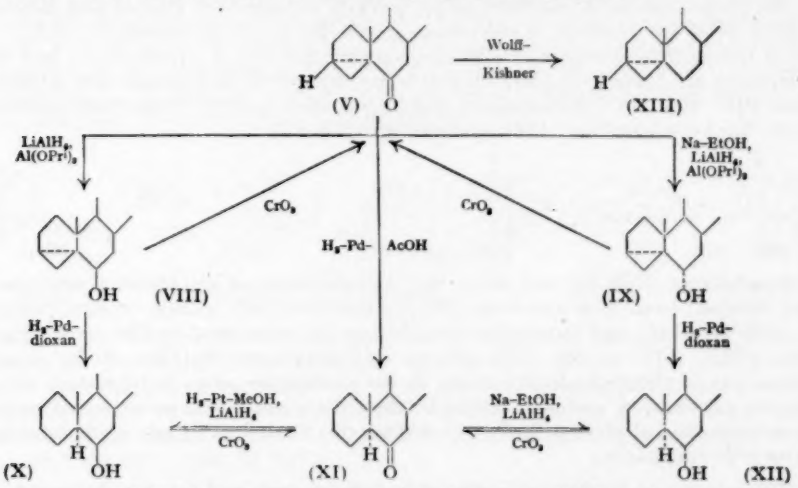
Contrariwise, the reaction (II ⟶ III) involves inversion of configuration at $C_{(3)}$, and 3 : 5-*cyclo*cholestane compounds contain a distorted *cis*-hexahydroindane structure. The configuration of the 3β-halogeno-ketones (IV; X = Cl, Br, or I) and 3β-toluene-*p*-sulphonyloxy-ketone (IV; X = *p*-C_6H_4·SO_2) is established (Shoppee, *J.*, 1948, 1032); these ketones, by ionic *trans*-elimination [*E*1 or *E*2], are converted quantitatively into *i*-cholestanone (3 : 5-*cyclo*cholestan-6-one) (V), which is obtained by oxidation of *i*-cholestan-6-ol (III) (formerly termed *i*-cholesterol), and can quantitatively be reconverted by the hydrogen halides into the 3β-halogeno-ketones (IV; X = Cl, Br, or I) (Heilbron, Hodges, and Spring, *J.*, 1938, 759; Wallis and Ford, *loc. cit.*; Ford, Chakravorty,

and Wallis, *loc. cit.*; Shoppee and Summers, *J.*, 1952, 1786). In a similar way, hydration of *i*-cholestanone (V) with dilute sulphuric acid in acetic acid gives 3β-hydroxycholestan-6-one (IV; X = OH) (Wallis, Fernholz, and Gephart, *loc. cit.*). It may be noted that the 3α-epimeric ketones (VI; X = Cl, Br, or *p*-$C_6H_4Me{\cdot}SO_2$) undergo 1 : 2-elimination with difficulty, to give poor yields of cholest-2-en-6-one (VII) (Ford, Chakravorty, and Wallis, *loc. cit.*; Blunschy, Hardegger, and Simon, *Helv. Chim. Acta*, 1946, **29**, 199; Riegel and Dodson, *J. Org. Chem.*, 1948, **13**, 424).



(IV; X = Cl, Br, I, or *p*-$C_6H_4Me{\cdot}SO_2$·) (V) (VI; X = Cl, Br, or *p*-$C_6H_4Me{\cdot}SO_2$·) (VII)

The 6-substituent in the derivatives (III) of 3 : 5-*cyclo*cholestane produced by the *i*-steroid rearrangement possesses the β-configuration. This result, which is probably general for 3 : 5-*cyclo*steroids, has been proved as follows. Hydrogenation of *i*-cholestanone (V) with palladium–acetic acid gives cholestan-6-one (XI) (Windaus, and Dalmer, *Ber.*, 1919, **52**, 162; Windaus and von Staden, *ibid.*, 1921, **54**, 1059; Ford, Chakravorty, and Wallis, *loc. cit.*; Heilbron, Hodges, and Spring, *J.*, 1938, 759), but when reduction is brought about by treatment with lithium aluminium hydride, little *i*-cholestanol (VIII) and much *epi-i*-cholestanol, m. p. 85—86°, $[\alpha]_D$ +83° (IX), are obtained. The latter substance has recently also been described (m. p. 86°, $[\alpha]_D$ +81°) by Wagner and Wallis (*J. Amer. Chem. Soc.*, 1950, **72**, 1047), and forms the only crystalline product isolated when reduction is effected with sodium–ethanol. It is difficult to obtain crystalline, but is oxidised by chromium trioxide to *i*-cholestanone (V), and smoothly converted by the appropriate halogen acid–acetic acid at 20°, into cholesteryl chloride, bromide, and iodide; its acetate, m. p. 60°, $[\alpha]_D$ +82°, appears to have been isolated but not identified by Heilbron, Hodges, and Spring (*J.*, 1938, 759) after acetylation of the product obtained by reduction of *i*-cholestanone with aluminium *iso*propoxide–*iso*propanol.

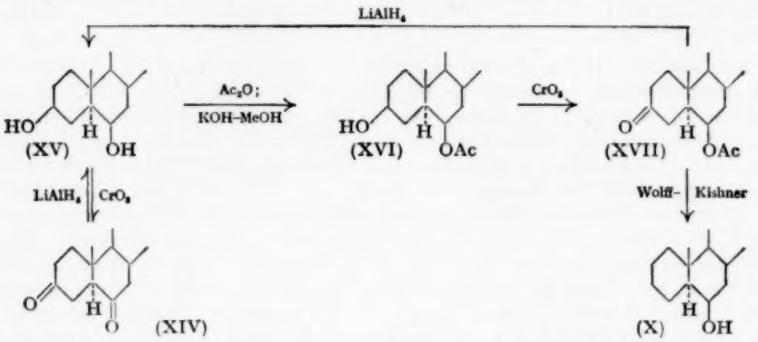


Low-pressure Wolff–Kishner reduction of *i*-cholestanone (V) gives *i*-cholestane (XIII), m. p. 78°, $[\alpha]_D$ +80°; this hydrocarbon, which gives a pale but distinct yellow colour with tetranitromethane, was described (m. p. 78—79°, $[\alpha]_D$ +80°), after our preparation of it, by Karrer and Schmid (*Helv. Chim. Acta*, 1949, **32**, 1371) and by Schmid and Kägi (*loc. cit.*).

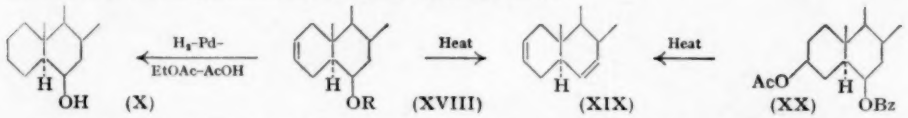
Hydrogenation of *i*-cholestanol (VIII) with palladium–dioxan in the presence of a *trace*

of acetic acid * affords, despite much hydrogenolysis leading to cholestane and an unidentified hydrocarbon, m. p. 61—65°, which is being investigated, cholestan-6β-ol (X), m. p. 82°, $[\alpha]_D$ +8°. Similar hydrogenation of *epi-i*-cholestanol (IX) gives cholestane and cholestan-6α-ol (XII), m. p. 129°, $[\alpha]_D$ +35°.

The substance (X) (acetate, m. p. 75°) is also obtained by hydrogenation of cholestan-6-one (XI) with platinum–methanol, and is identical with the compound obtained by reduction with zinc of 3β-iodocholestan-6β-ol, in which the β-configuration of the hydroxyl group is indicated by its ready ionic 5 : 6-*trans*-dehydration to cholesteryl iodide (Shoppee and Summers, *J.*, 1952, 1786). It has also been obtained from cholestane-3 : 6-dione (XIV); this by reduction with lithium aluminium hydride gives cholestane-3β : 6β-diol (XV), which by acetylation and partial hydrolysis furnishes the 6-monoacetate (XVI), oxidised by chromium trioxide to 6β-acetoxycholestan-3-one (XVII), which regenerates



the diol (XV) by lithium aluminium hydride reduction, and affords cholestan-6β-ol (X) by low-pressure Wolff–Kishner reduction. Finally, cholestan-6β-ol (X) is obtained by hydrogenation of cholest-2-en-6β-ol (XVIII; R = H); this substance, whose preparation is described in the following communication, by pyrolysis as the benzoate (XVIII; R = Bz) gives cholesta-2 : 6-diene (XIX), recently obtained by Barton and Rosenfelder (*J.*, 1950, 2459) by pyrolysis of cholestane-3β : 6β-diol 3-acetate 6-benzoate (XX). Since thermal elimination reactions require *cis*-geometry (Barton, *J.*, 1949, 2174), and steroid 6β-benzoates are known to yield cholest-6-enes by pyrolysis (Barton and Rosenfelder, *Nature*, 1949, **164**, 316; Wintersteiner and Moore, *ibid.*, p. 316), these observations again indicate the β-configuration of the hydroxyl group in (X).



The substance (XII) (acetate, m. p. 95°) is cholestan-6α-ol and identical with the compound obtained from cholestan-6-one (XI) by reduction with sodium–ethanol (Tschesche, *Ber.*, 1932, **65**, 1842), and incorrectly described as cholestan-6β-ol in Elsevier's "Encyclopaedia" (Vol. XIV, p. 66). The greater thermodynamic stability of the equatorial conformation of the 6α-hydroxyl group in the cholestane series is consistent with this method of preparation, and is indicated by the partial conversion by extended treatment with sodium–amyl alcohol at 200° of cholestane-3β : 6β-diol (XV) into cholestane-3β : 6α-diol (see following paper).

* Hydrogenation of *i*-cholestanyl acetate with platinum–acetic acid furnishes cholestanyl acetate (Wallis, Fernholz, and Gephart, *loc. cit.*), probably as a consequence of rearrangement induced by the high concentration of acetic acid (see p. 3366) to cholesteryl acetate and reduction of this. Hydrogenation of *i*-cholestanyl methyl ether with platinum–acetic acid to a compound, $C_{28}H_{50}O$, m. p. 78°, which depressed the m. p. (82·5—83°) of cholestanyl methyl ether and was stable to hydrochloric acid at 100°, has been reported (Wagner–Jauregg and Werner, *loc. cit.*); the production of 6β-methoxycholestane under these conditions would not be expected and the matter is being investigated.

Reduction of cholestan-6-one (XI) with lithium aluminium hydride furnishes a mixture of cholestan-6β-ol (X) (95%) and cholestan-6α-ol (XII) (5%) which may be separated chromatographically.

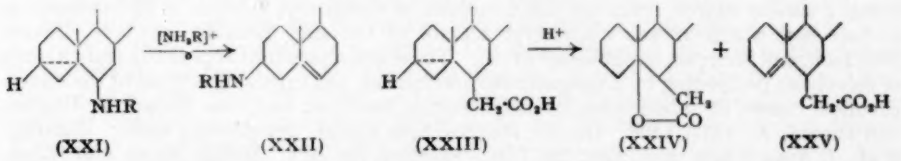
Finally, the configurations assigned chemically to the epimeric cholestan-6-ols are confirmed physically by the agreement shown by the molecular rotations observed by us and those calculated by the method of molecular rotation differences (Barton and Klyne, *Chem. and Ind.*, 1948, 755):

Cholestan-6α-ol (XII)	$[M]_D$ (obs.) + 136°	$[M]_D$ (calc.) + 147°
Cholestan-6β-ol (X)	„ + 31	„ + 39

These results show that *i*-cholestanol is 3 : 5-*cyclo*cholestan-6β-ol, and suggest that other *i*-steroids formed from 3β-hydroxy-Δ^5-steroids are 6β-substituted compounds.

From the first reaction scheme (p. 3362) it will be seen that in media which become increasingly acidic as solvolysis proceeds derivatives of cholesterol are produced, but that in buffered media 3 : 5-*cyclo*cholestane derivatives are formed in high yield.* There is one exception to this generalisation; acetolysis in the presence of acetate ion furnishes *only* cholesteryl acetate. This fact is clearly related to the observations that 6β-methoxy-3 : 5-*cyclo*cholestane and 6β-methoxy-3 : 5-*cyclo*stigmast-22-ene, when heated with potassium or zinc acetate in acetic acid, undergo quantitative conversion into cholesteryl and stigmasteryl acetate respectively (Heilbron *et al.*, *J.*, 1936, 907; Fernholz and Ruigh, *J. Amer. Chem. Soc.*, 1940, **62**, 3346).

3 : 5-*cyclo*Steroids are sensitive to acids. 6β-Methoxy-3 : 5-*cyclo*cholestane is hydrolysed (and rearranged to cholesterol) under conditions in which cholesteryl methyl ether (II) is completely stable (Wagner-Jauregg and Werner, *loc. cit.*; Heilbron *et al.*, *locc. cit.*); it has been shown to react with alcohols (McKennis, *loc. cit.*; Winstein and Schlesinger, *loc. cit.*), with alkanethiols (Ralls, Dodson, and Riegel, *J. Amer. Chem. Soc.*, 1949, **71**, 3320), with pyridine, and with thiourea (King, Dodson, and Sablusky, *ibid.*, 1948, **70**, 1176) in the presence of small quantities of toluene-*p*-sulphonic acid, to give cholesteryl alkyl ethers, cholesteryl ethyl sulphide, cholesteryl pyridinium and thiuronium salts respectively. These acid-catalysed reactions probably involve addition of a proton, or in pyridine of the pyridinium cation $[PyH]^+$, which functions as an acid like $[NH_4]^+$ in liquid ammonia, to a lone pair of the oxygen atom of the methoxyl group. Similarly, 6β-amino-3 : 5-*cyclo*steroids (XXI; R = Ph or CH_2Ph) in aniline or benzylamine in the presence, but not in the absence, of the appropriate cation $[NH_3R]^+$ undergo rearrangement to substituted cholesterylamines (XXII) after attack at the lone pair of electrons on the nitrogen atom (Julian, Magnani, Meyer, and Cole, *ibid.*, p. 1834).



(XXI) (XXII) (XXIII) (XXIV) (XXV)

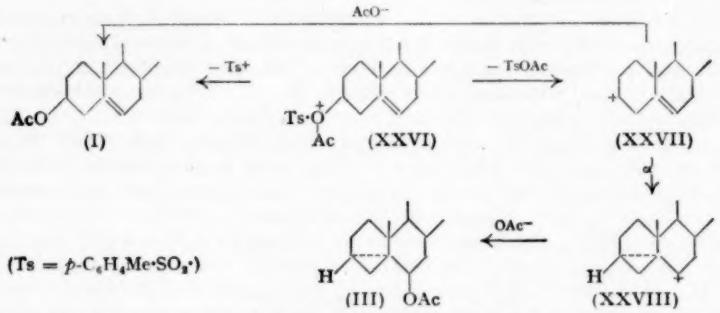
If the $C_{(6)}$-substituent in a 3 : 5-*cyclo*steroid possesses no lone pair of electrons, rearrangement to a cholest-5-ene derivative does not take place; 3 : 5-*cyclo*cholestanyl-6β-acetic acid (XXIII) by treatment with dilute sulphuric acid–acetic acid yields a lactone, formulated as the 6β→5β-lactone † (XXIV), accompanied by a dehydration product formulated as the cholest-4-ene-6β-acetic acid † (XXV) (Kaiser and Svarz, *ibid.*, 1945, **67**, 1309; 1947, **69**, 847; 1949, **71**, 517).

* Compare the discussion of the reaction of cholesteryl chloride with alcohols in presence of etched magnesium given by Wagner-Jauregg and Werner (*loc. cit.*); the reversion of 3 : 5-*cyclo*cholestan-6β-ol to 3β : 5α : 6β-tribromocholestane with bromine in ether (Heilbron *et al.*, *loc. cit.*) is curious and noteworthy as occurring in an apparently neutral medium.

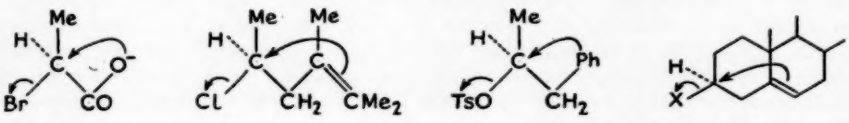
† Alternatively, these compounds may be formulated as a 6β→3β-lactone and a cholest-2-ene-6β-acetic acid, or, by fission of the $C_{(4)}$–$C_{(5)}$-bond (cf. Schmid and Kägi, *loc. cit.*), as 3-methyl-5β-hydroxy-A-norcholestane-6β-acetic acid 6β→5β-lactone and 3-methyl-A-norcholest-3(5)-ene-6β-acetic acid.

The apparently anomalous action of acetic acid or its conjugate acid $[AcOH_2]^+$ seems to depend on concentration; by contrast with the solvolysis of (II) conducted in acetic acid with or without added acetate ion, a solvolysis in an alcohol proceeding in the presence of acetate ion can give rise to only one molecular proportion of acetic acid. Experiments are being made to determine the rate of rearrangement of 3 : 5-*cyclo*steroids as a function of the acetic acid concentration.

Solvolysis of cholesteryl toluene-*p*-sulphonate with acetic anhydride–potassium acetate gives both cholesteryl acetate (I) and 3 : 5-*cyclo*cholestan-6β-yl acetate (III), together with an unsaturated hydrocarbon, probably cholesta-3 : 5-diene. We find that cholesteryl chloride behaves similarly. The results suggest that a carbonium ion (XXVII) is produced, which can undergo either elimination [*E*1] to give cholesta-3 : 5-diene, or rearrangement to a second carbonium ion (XXVIII) which furnishes the acetate (III). Acetic anhydride undergoes ionisation: $Ac_2O \rightleftharpoons Ac^+ + OAc^-$ (Mackenzie and Winter, *Trans. Faraday Soc.*, 1948, **44**, 161), and in the presence of potassium acetate an active entity will also be the ion $[Ac_2OK]^+ = Ac^+ + KOAc$ (Burton and Praill, *J.*, 1950, 1203), so that as suggested privately by Professor Burton in the case of the toluene-*p*-sulphonate, reaction with the acetylium ion can give (XXVI) which by acyl–oxygen fission furnishes only cholesteryl acetate (I), but by alkyl–oxygen fission affords the carbonium ion (XXVII), which may or may not rearrange to (XXVIII) before attack by an acetate ion. A similar scheme for cholesteryl chloride would involve a chloronium ion as an intermediate.



The acetolysis of cholesteryl toluene-*p*-sulphonate with or without acetate ion is kinetically of the first order (Winstein and Adams, *J. Amer. Chem. Soc.*, 1948, **70**, 838); we have confirmed this and have identified the product as cholesteryl acetate; we have found a similar kinetic result for the acetolysis of cholesteryl bromide in the presence of acetate ion, which affords cholesteryl acetate as the sole isolatable product (Davies, Meecham, and Shoppee, unpublished work). These acetolyses thus appear to fit into a series of solvolyses proceeding by a unimolecular mechanism and involving control of the stereochemical course of substitution by neighbouring unshared electrons (Cowdrey, Hughes, and Ingold, *J.*, 1937, 1208; Davies, Hughes, and Ingold, unpublished work; Winstein, *et al.*, *J. Amer. Chem. Soc.*, 1952, **74**, 1140; Shoppee, *loc. cit.*). Wallis, Hafez, and Halsey



Reaction:

Methanolysis Hydrolysis Formolysis Acetolysis

(In all cases the reaction is of first order and has S_N1 mechanism, and there is retention of configuration at the seat of substitution.)

(*loc. cit.*) also found a first-order rate constant for the hydrolysis of cholesteryl toluene-*p*-sulphonate in aqueous acetone in the presence of acetate ion and showed that the rate of

hydrolysis increased with increasing ease of separation of the 3β-substituent as the anion : p-$C_6H_4Me{\cdot}SO_3^- < Ph{\cdot}SO_3^- < p$-$NO_2{\cdot}C_6H_4{\cdot}SO_3^-$; this sequence is consistent with a reaction of S_N1 type, but the product is known to be largely 3 : 5-*cyclo*cholestan-6β-ol (Beynon, Heilbron, and Spring, *J.*, 1937, 1459). Clearly the main sequel here to formation of a carbonium ion is rearrangement followed by addition of an anion so that the situation has some analogies with the Wagner change (cf. Dostrovsky, Hughes, and Ingold, *J.*, 1946, 192).

There are three mechanistic possibilities for the conversion of cholest-5-ene compounds into 3 : 5-*cyclo*steroids. Mechanism 1 involves participation of the π-electrons of the double bond *subsequently* to the rate-determining ionisation of the 3β-substituent; it postulates the existence of the cholest-5-enyl cation and the 3 : 5-*cyclo*cholestanyl cation as individual stereochemical entities separated by an energy hill of height sufficient to preclude interaction. Mechanism 2 involves participation *simultaneously* with the rate-determining ionisation, which is thereby facilitated, leading to the formation of a mesomeric ion. The canonical forms of a mesomeric ion are believed not to exist as separate chemical entities and must be distinguished from the isomeric cations of mechanism 1; the picture here is that of the hypothetical canonical structures * separated by an energy valley and interacting to produce a more stable structure. This mechanism has been considered without regard to stereochemical implications by Shoppee (*Ann. Reports*, 1947, **44**, 173), Winstein and Adams, Winstein and Schlesinger, and Hafez, Halsey, and Wallis (*locc. cit.*). In both these mechanisms, the reaction will be of first order with respect to the steroid molecule and zero order with respect to the reactant anion, and so will exhibit overall first-order kinetics. Mechanism 3 involves participation of the π-electrons in a *synchronous* bond-forming bond-breaking process leading *via* a linear transition state to inversion at $C_{(3)}$ and introduction of a new anion at $C_{(6)}$. It has been envisaged as operating under appropriate conditions by Winstein and Schlesinger (*loc. cit.*), when it will exhibit second-order kinetics, but it does not seem to offer an explanation of the stereospecificity of the 3 : 5-*cyclo*steroid rearrangement at $C_{(6)}$.

It is difficult to distinguish between mechanisms 1 and 2. Formation of cholesta-3 : 5-diene suggests the real existence of the cholest-5-enyl cation as in mechanism 1, although formation of 3 : 5-*cyclo*cholest-6-ene [the *i*-cholestadiene of Riegel, Hager, and Zenitz (*J. Amer. Chem. Soc.*, 1946, **68**, 2562)] from the 3 : 5-*cyclo*cholestanyl cation, if this exists as a separate entity, has not been observed; on the other hand, the increased reactivity of cholest-5-enyl compounds compared with their cholestanyl analogues supports mechanism 2. It is however possible, by using either mechanism 1 or mechanism 2, to give an explanation of the phenomena of the 3 : 5-*cyclo*steroid rearrangement in terms of the thermodynamic and kinetic control of equilibria.

It is difficult to assess the thermodynamic stabilities of the isomeric Δ^5-steroid and 3 : 5-*cyclo*steroid molecules, and the relative stabilities of their carbonium ions and the reactivities of these to nucleophilic reagents. The thermodynamic stability of the cholest-5-ene molecule has been estimated to exceed that of 3 : 5-*cyclo*cholestane by some 7 kcal. (Roberts *et al.*, *ibid.*, 1950, **72**, 3116); and we hope shortly to report a determination of the heats of combustion of 3β-methoxycholest-5-ene and 6β-methoxy-3 : 5-*cyclo*cholestane. There is no evidence as to the relative stability of the Δ^5-cation and the 3 : 5-*cyclo*-cation but it seems probable that they are not greatly different; the Δ^5-cation possesses as a major factor of stability conjugation of the π-electrons with the cationic centre at $C_{(3)}$, whilst if the 3 : 5-bond is regarded as a partial and modified linkage of sp^2 type (Walsh, *Trans. Faraday Soc.*, 1949, **45**, 179; cf. however, Coulson and Moffitt, *J. Chem. Phys.*, 1947, **15**, 151) there will be similar if somewhat less effective conjugation in the 3 : 5-*cyclo*-cation. The contribution of hyperconjugation to these stabilities will be small. If we assume that the transition state for the ionic recombination, Δ^5-cation ⟶ Δ^5-molecule, lies energetically

* The canonical structures appear to differ in regard to the position of the hydrogen nucleus at $C_{(3)}$ and so to break the rules relating to resonance hybrids; this difficulty is probably more apparent than real. Just as in benzene a compression energy of 33 kcal. is required to deform the structure of a Kékulé individual to a canonical structure capable of resonance with an energy of 40 kcal., so here a compression energy is required to deform the structure so that the hydrogen nucleus occupies a mean position and the distance between $C_{(3)}$ and $C_{(5)}$ is reduced from about 2·5 to 1·5 Å (cf. Coulson and Altmann, *Trans. Faraday Soc.*, 1952, **48**, 293).

higher than that for the ionic recombination : 3 : 5-*cyclo*-cation ⟶ 3 : 5-*cyclo*-molecule, it becomes possible to explain the occurrence of the 3 : 5-*cyclo*steroid rearrangement in terms of a symbolic energy diagram (Fig. *A*) (cf. Catchpole, Hughes, and Ingold, *J.*, 1948, 11).

In Fig. *A* the reaction path enters from the left; in a medium, which is neutral or maintained near neutrality by buffering with acetate ion, a Δ^5-steroid molecule ionises to give the Δ^5-ion, which may either reassociate slowly with an external anion, or rearrange with some loss of free energy to give the 3 : 5-*cyclo*-cation, which rapidly combines with an external anion to give the 3 : 5-*cyclo*-steroid molecule. Despite the lesser thermodynamic stability of the 3 : 5-*cyclo*-steroid, it may thus be formed as the main or even as the sole reaction product as a result of kinetic control of the equilibria. If these conditions obtain for a sufficiently long time, thermodynamic control of the equilibria must eventually furnish Δ^5-steroid molecules if the disparity between (*a*) the energies of the two cations and (*b*) the speeds of their anionic recombination is not too great; a sufficient period in a polar solvent of large dielectric constant might in favourable circumstances be expected to permit the conversion of 3 : 5-*cyclo*steroid into Δ^5-steroid, but we were unable to convert 6β-methoxy-3 : 5-*cyclo*cholestane into 3β-methoxycholest-5-ene by heating it in methyl cyanide (dielectric constant, 37·5) at 82° for long periods. Under acid conditions any

FIG. *A*.

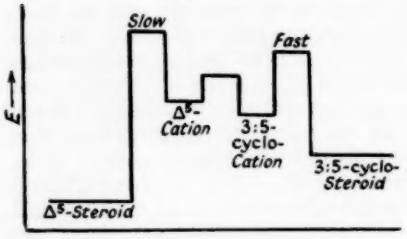
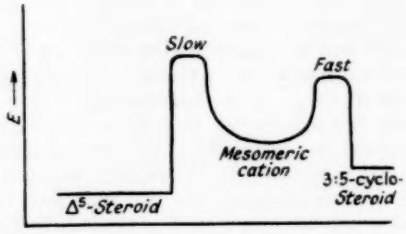


FIG. *B*.



3 : 5-*cyclo*steroid molecule, formed by traversing the reaction path completely from left to right, will continually be attacked by protons or their conjugates and so re-ionised to give the 3 : 5-*cyclo*-cation and rearranged to the Δ^5-cation, eventually to yield the Δ^5-steroid molecule. The instability of the 3 : 5-*cyclo*steroid molecule to acids thus enables the thermodynamic control of equilibria to become effective; in a limited time and in the presence of a very small concentration (0·001M) of toluene-*p*-sulphonic acid, 6β-methoxy-3 : 5-*cyclo*cholestane in ethanol at 78° gives 68% of 6β-ethoxy-3 : 5-*cyclo*cholestane and 32% of 3β-ethoxycholest-5-ene together with some unaltered material (Winstein and Schlesinger, *loc. cit.*). This result clearly indicates the initial conversion of the 6β-methoxy-3 : 5-*cyclo*cholestane into the analogous ethoxy-compound; this may be represented in Fig. *A* by considering the reaction path entering from the right, traversing the lower heterolytic transition state, and returning by the same route.

Fig. *A*, which was drawn early in 1951 and formed part of the manuscript of a contribution to the Steroid Symposium held by the American Chemical Society in September, 1951, bears a close resemblance to a broken-line diagram given subsequently by Brown, Hughes, Ingold, and Smith (*Nature*, 1951, **168**, 65, Fig. 2) to illustrate certain aspects of the Wagner change. Just as Fig. *A* illustrates mechanism 1 for the 3 : 5-*cyclo*steroid rearrangement, so Fig. *B*, which is analogous to the full line diagram (Fig. 2) of Hughes, Ingold, *et al.*, can be drawn to illustrate mechanism 2 (involving a mesomeric cation) for the 3 : 5-*cyclo*steroid rearrangement. Both mechanisms are consistent with the facts cited previously in this paper and with the observations that 6β-acetoxy-3 : 5-*cyclo*cholestane can readily be obtained from the parent alcohol, although the 3 : 5-dinitrobenzoate is always accompanied by some cholesteryl 3 : 5-dinitrobenzoate (Wallis, Fernholz, and Gephart, *loc. cit.*), whilst 6β-chloro-3 : 5-*cyclo*cholestane seems incapable of preparation [tendency to separate as anion : $OAc^- < (NO_2)_2{\cdot}C_6H_4{\cdot}CO_2^- \ll Cl^-$], and that lithium

aluminium hydride reduction of cholesteryl toluene-*p*-sulphonate gives both cholest-5-ene and 3 : 5-*cyclo*cholestane (Karrer and Schmid, *loc. cit.*). Fortunately, either mechanism gives a reasonable explanation of the stereochemistry of the 3 : 5-*cyclo*steroid rearrangement.

Figures *C*, *D*, and *E* represent diagrammatic views, vertically down the $C_{(5)}$–$C_{(10)}$ bond axis in the general plane of the ring system and without regard to geometric detail,* of the Δ^5-cation, the 3 : 5-*cyclo*-cation, and the mesomeric cation. Knowledge of the retention of configuration in substitution reactions at $C_{(3)}$ in Δ^5-steroids (Shoppee, *J.*, 1946, 1147) shows that the charge cloud resulting from the π-electrons of the double bond has maximum density at the α-face of $C_{(3)}$ (Fig. *C*); this must clearly also be the case for the α-face of $C_{(6)}$ (Fig. *D*), and for the α-faces of $C_{(3)}$, $C_{(5)}$, and $C_{(6)}$ in the mesomeric cation (Fig. *E*). When the 3 : 5-*cyclo*-cation represented by (*D*) combines with an anion, or when the distributed charge of the mesomeric cation represented by (*E*) becomes concentrated at $C_{(6)}$ coordination of an anion will furnish the 6β-configuration. A somewhat similar argument

FIG. *C*. FIG. *E*. FIG. *D*.

has been used by Dodson and Riegel (*J. Org. Chem.*, 1948, **13**, 424). The suggestion of Winstein and Adams (*loc. cit.*) that substitutions at $C_{(3)}$ take place by way of 3 : 5-*cyclo*-steroids, so that the observed complete retention of configuration at $C_{(3)}$ is the result of two successive inversions, Δ^5-steroid $\xrightarrow{-s}$ 3 : 5-*cyclo*-steroid $\xrightarrow{-s}$ Δ^5-steroid, cannot be excluded; it appears, however, to be difficult to apply this proposal to the replacement of hydroxyl by chlorine in the conversion of cholesterol into cholesteryl chloride by hydrogen chloride (Shoppee and Summers, *J.*, 1952, 1786).

The conversion of *both* 3 : 5-*cyclo*cholestan-6β- and -6α-ol into cholesterol in acidic media, reported by Wagner and Wallis (*loc. cit.*) and confirmed by us, is consistent with the foregoing stereochemical picture. It does not seem to furnish a means of distinguishing between mechanism 1 and mechanism 2; in the mesomeric cation (*E*) both $C_{(3)}$ and $C_{(6)}$ will possess trigonal sp^2-configurations, so that both the 6-epimerides will afford the same structure, whilst if the Δ^5-cation (*C*) and the 3 : 5-*cyclo*-cation (*D*) are separate structures with maintained tetrahedral sp^3-configurations only the 3 : 5-*cyclo*-cation represented by (*D*) will exist. For if an epimeric 3 : 5-*cyclo*-cation with a β-orientated hydrogen atom at $C_{(6)}$ were to arise from 3 : 5-*cyclo*cholestan-6α-ol, the influence of the electron cloud derived from the 3 : 5-bond might be expected to lead at once to inversion at $C_{(6)}$ with production of the 3 : 5-*cyclo*-cation represented by (*D*).

EXPERIMENTAL

M. p.s were determined thermo-electrically on a Kofler block; limit of error ±2°. Solvents for chromatographic operations were rigorously purified and dried and, unless stated otherwise, aluminium oxide (Spence type H, activity ~II) was used. For drying of ethereal extracts, brief treatment with anhydrous sodium sulphate was used. [α] refers to chloroform solutions.

Cholestan-6-one (XI).—This ketone was obtained as described by Windaus (*Ber.*, 1919, **52**, 162) and by Shoppee and Summers (*J.*, 1952, 1786); we examined a modification of the route used by Riegel and Dodson (*J. Org. Chem.*, 1948, **13**, 424) involving nitration of cholesteryl acetate (Mauthner and Suida, *Monatsh.*, 1903, **24**, 648; cf. Heilbron *et al.*, *J.*, 1938, 104, and Fieser and Rigaudy, *J. Amer. Chem. Soc.*, 1951, **73**, 4660); this at first gave variable results, but the following procedure appears satisfactory. Finely powdered cholesteryl acetate (m. p. 115°; 20 g.) was added to nitric acid (300 c.c.; *d* 1·42) rapidly stirred at 20°; powdered potassium nitrite (2 g.) was then added and a remarkable change occurred. Nitrogen oxides were evolved and simultaneously the cholesteryl acetate was transformed into a flocculent material which later became crystalline; the reaction appeared to be almost instantaneous. Stirring was continued for 1 hour, the nitric acid removed by filtration, and the reaction product digested

* In Δ^5-steroids ring A is a chair form, whilst in 3 : 5-*cyclo*steroids ring B also has the chair conformation.

with a large volume of water, filtered, washed very thoroughly with water, and dried on porous porcelain and finally in a vacuum desiccator (yield, 21 g.). The crude dry product by crystallisation from ethanol gave 3β-acetoxy-6-nitrocholest-5-ene in prismatic needles, m. p. 103° (18·3 g., 80%). The ketone (XI) was also obtained (*a*) from 3β-chloro-6-nitrocholest-5-ene by prolonged reduction with zinc–acetic acid (cf. Windaus and von Staden, *Ber.*, 1921, **54**, 1059) and chromatographic separation from 3β-chlorocholestan-6-one, and (*b*) from 3β-bromo-6-nitrocholest-5-ene.

Cholesteryl bromide (m. p. 98°; 4 g.) was stirred at 20° with concentrated nitric acid (*d* 1·42; 30 c.c.) and fuming nitric acid (*d* 1·54; 50 c.c.), and powdered sodium nitrite (3 g.) was added gradually during 10 minutes; stirring was continued for 0·75 hour at 20°. The solid yellow product was filtered off on sintered glass, washed with much water and with ethanol, dried on porous porcelain, and crystallised from acetic acid, to give 3β-bromo-6-nitrocholest-5-ene as needles, m. p. 153° (cf. Vanghelovici and Angelescu, *Bull. Soc. chim. România*, 1935, **17**, 251). The nitro-compound (1·5 g.) was heated under reflux with zinc dust (2 g.) in acetic acid for 2 hours. The solution was poured into water and extracted with benzene. After being washed to neutrality and dried in the usual way, the extract by evaporation gave an oil, which after filtration of a pentane solution through a column of aluminium oxide, crystallised from methanol, in plates, m. p. 96—98°, undepressed by admixture with authentic cholestan-6-one.

Cholestan-6β-*ol* (X).—(*a*) Cholestan-6-one (XI) (102 mg.) dissolved in methanol (or ethanol) (10 c.c.) was hydrogenated at 30° in the presence of platinum oxide (60 mg.); absorption of 1 mol. of hydrogen required 8 hours. The catalyst was removed and the filtrate evaporated completely in a vacuum. The residue was chromatographed on alumina (4 g.) prepared in pentane, eluates of 5 c.c. each being examined. The material from fractions 1—4 (eluant, pentane; 27 mg.; an oil which, crystallised from ether–methanol, had m. p. 79—80°) was cholestane and did not depress the m. p. of an authentic specimen. From fractions 11—16 (eluant, 1 : 1-benzene–pentane; total 53 mg. of oil) was obtained *cholestan*-6β-*ol*, m. p. 80—82°, $[\alpha]_D$ +8°±2° (*c*, 0·602) [Found, after drying at 60—65°/0·01 mm. for 3 hours: C, 83·0; H, 12·4. $C_{27}H_{48}O$ requires C, 83·4; H, 12·4%).

(*b*) To a solution of lithium aluminium hydride (1·7 g.) in boiling ether (200 c.c.) was added dropwise a solution of cholestan-6-one (3·5 g.) in ether (200 c.c.) at a rate sufficient to keep the ether gently refluxing. After 20 minutes the reaction was stopped, the reaction mixture cooled in ice, and ice-cold 2N-sulphuric acid added carefully to destroy excess of the reducing agent. The ethereal solution was washed with 2N-sulphuric acid, and with water to neutrality (litmus), dried, and evaporated. The resultant colourless oil (3·5 g.) was chromatographed on aluminium oxide (110 g.) prepared in pentane, eluates of 300 c.c. each being collected. Fractions 1—4 (eluant, pentane) furnished unchanged cholestan-6-one (60 mg. of m. p. 92—96°), m. p. 96—98° after recrystallisation from acetone. Fractions 11—23 (eluant, 1 : 9 ⟶ 1 : 1 benzene–pentane) were united (total, 3·25 g.; m. p. 71—75°) and recrystallised from methanol, to give cholestan-6β-ol in prisms, m. p. 79—81°, giving no depression with the material obtained by method (*a*). The material from fractions 26—29 (eluant, 1 : 9 ether–benzene) consisted of cholestan-6α-ol (230 mg.), m. p. 127° after recrystallisation from methanol; it gave no depression with authentic cholestan-6α-ol (see below).

Cholestan-6β-ol (100 mg.), dissolved in acetic acid (2 c.c.) and oxidised with chromium trioxide (2 c.c. of a 2% solution in acetic acid) for 15 hours at 20°, gave by the usual procedure cholestan-6-one as plates (from methanol), m. p. 96—97°. The *acetate*, prepared by use of acetic anhydride–pyridine at 100° for 3 hours and isolated in the usual way, crystallised from methanol in needles, m. p. 75°, $[\alpha]_D$ −7·5°±1° (*c*, 2·497) (Found, after drying at 20°/0·05 mm. for 20 hours: C, 81·0; H, 11·9. $C_{29}H_{50}O_2$ requires C, 80·9; H, 11·7%). Benzoylation with benzoyl chloride–pyridine at 20° for 24 hours, followed by working up in the usual way, gave the *benzoate* as prismatic needles (from acetone), m. p. 79—80° (Found, after drying at 20°/0·05 mm. for 8 hours: C, 82·7; H, 10·4. $C_{34}H_{52}O_2$ requires C, 82·9; H, 10·6%).

Cholestan-6α-*ol* (XII).—This was prepared by the reduction of cholestan-6-one with sodium–ethanol according to the directions of Tschesche (*Ber.*, 1932, **65**, 1842) and had m. p. 129—130° after crystallisation from methanol. The acetate prepared by acetic anhydride–pyridine at 20° had m. p. 96°. Benzoylation as above gave the *benzoate* as prismatic needles (from acetone–methanol), m. p. 103—105°, $[\alpha]_D$ +62·5°±3° (*c*, 1·045) (Found, after drying at 20°/0·05 mm. for 8 hours: C, 82·5; H, 10·3%). The toluene-*p*-sulphonate, prepared by use of toluene-*p*-sulphonyl chloride–pyridine for 15 hours at 25°, crystallised from acetone–pentane in very thin needles m. p. 109—110°, $[\alpha]_D$ +68°±2° (*c*, 2·484) (cf. Karrer *et al.*, *Helv. Chim. Acta*, 1951, **34**, 1022, who give m. p. 108·5—110°, $[\alpha]_D$ +64° in chloroform).

3 : 5-cyclo*Cholestan-6-one* (VIII).—This was prepared (cf. Dodson and Riegel, *J. Org. Chem.*, 1948, **13**, 424) by heating 3β-chlorocholestan-6-one with refluxing 5% ethanolic potassium hydroxide for 0·5 hour, purified by filtration of a pentane solution through alumina and by recrystallisation from methanol, the compound having m. p. 96°. Hydrogenation with palladium oxide–acetic acid at 25° gave crude cholestan-6-one, m. p. 88—92°, raised by chromatography and subsequent recrystallisation from acetone to 96—97·5°.

3 : 5-cyclo*Cholestan-6β-ol* (VIII) ***and* 3 : 5-cyclo*Cholestan-6α-ol*** (IX).—(*a*) **3 : 5-*cyclo*Cholestan-6-one** (V) (1·24 g.) in ether (150 c.c.) was added during 1 hour to a solution of lithium aluminium hydride (2·32 g.) in boiling ether (300 c.c.); refluxing was continued for 1·5 hours. The ethereal solution was treated with ice-water at 0° and cold 2N-sulphuric acid, washed with sodium hydrogen carbonate and with water, dried, and evaporated. The resultant oil (1·2 g.) was chromatographed on alumina (35 g.), 120 c.c. eluates being collected (see Table).

Fraction	Eluant	Eluates
1—6	Pentane	Cryst. (13 mg.), m. p. 92—96°, 3 : 5-*cyclo*cholestan-6-one
7—9	Benzene–pentane (1 : 19)	Oil (3 mg.)
10—12	Benzene–pentane (1 : 9)	Crystd. spontaneously (25 mg.), m. p. 81—84°, 3 : 5-*cyclo*cholestan-6α-ol
13—18	Benzene–pentane (1 : 4)	Oil (200 mg.)
19—23	Benzene–pentane (1 : 1)	Oil (220 mg.)
24—28	Benzene	Oil (525 mg.)
29—31	Ether–benzene (1 : 19)	Oil (125 mg.), crystd. from methanol at −10°, m. p. 70—74°, 3 : 5-*cyclo*cholestan-6β-ol

A further quantity of **3 : 5-cyclo*cholestan-6α-ol*** (IX) was obtained as follows. Fractions 13—23 were distilled in a molecular flask at 120—134°/0·01 mm. but the distillate failed to crystallise and was rechromatographed on a long column of alumina (65 g.) and eluted continuously with benzene–pentane (1 : 9). The material so obtained was distilled in a molecular flask at 120—130°/0·01 mm.; the distillate (400 mg.) crystallised at once when cooled and moistened with pentane, and had m. p. 85—86°, $[\alpha]_D$ +83°±3° (*c*, 0·714) (Found, after drying at 20°/0·01 mm. for 3 hours: C, 84·1; H, 12·2. $C_{27}H_{46}O$ requires C, 83·9; H, 12·0%); the m. p. was depressed to 59° by admixture with **3 : 5-*cyclo*cholestan-6β-ol** (VIII), m. p. 74°. Similar treatment of fractions 24—28 failed to yield crystalline material. Fractions 29—31 yielded **3 : 5-*cyclo*cholestan-6β-ol** (VIII), m. p. 71—74°, undepressed by admixture with a genuine specimen.

(*b*) **3 : 5-*cyclo*Cholestan-6-one** (V) (365 mg.) in ethanol (30 c.c.) was heated on a steam-bath with sodium (2·6 g.). After dissolution of the sodium, the reaction mixture was poured into water, ethanol partly removed in a vacuum, and the product isolated as an oil (320 mg.) which was chromatographed on alumina (9 g.) prepared in pentane. Only the fractions obtained by elution with benzene–pentane (1 : 9) could be caused to crystallise; by cooling of a solution in acetone at −10° plates, m. p. 78—86°, were obtained which recrystallised readily from acetone after inoculation, to yield **3 : 5-*cyclo*cholestan-6α-ol** (140 mg.), m. p. 85—86°, giving no depression by admixture with the specimen prepared by method (*a*). Acetylation of the new alcohol with acetic anhydride–pyridine at 20° for 15 hours, followed by the usual working up, gave an oily acetate; alkaline hydrolysis regenerated the parent alcohol.

3 : 5-cyclo*Cholestan-6-one* (V) ***from* 3 : 5-cyclo*Cholestan-6α-ol*** (IX).—**3 : 5-*cyclo*Cholestan-6α-ol** (10 mg.) in acetic acid (0·5 c.c.) was treated with 2% solution of chromium trioxide in acetic acid (0·5 c.c.) at 20° for 15 hours; the product, isolated in the usual manner as an oil, was purified by passage of its solution in pentane through aluminium oxide (300 mg.), to give **3 : 5-*cyclo*cholestan-6-one**, m. p. 92—95°, which did not depress the m. p. of an authentic sample.

Cholesteryl Chloride, Bromide, and Iodide from* 3 : 5-cyclo*Cholestan-6α-ol (IX).—Treatment of **3 : 5-*cyclo*cholestan-6α-ol** with hydrogen chloride, hydrogen bromide, or hydrogen iodide in acetic acid at 20° for 3 hours (cf. Beynon, Heilbron, and Spring, *J.*, 1936, 907) gave cholesteryl chloride, bromide, and iodide respectively in quantitative yield.

Cholestan-6β-ol (X) ***from* 3 : 5-cyclo*Cholestan-6β-ol*** (VIII).—**3 : 5-*cyclo*Cholestan-6β-ol** (220 mg.), dissolved in dioxan (15 c.c.) containing a trace of acetic acid (0·75 c.c.), was shaken with palladium oxide (150 mg.; not freshly prepared) in an atmosphere of hydrogen at 30°. After an induction period of about 2 hours, hydrogen was absorbed and absorption was allowed to proceed until 1 mol. had been taken up. After separation of the catalyst and removal of the solvent under reduced pressure, an oily product was obtained which tended to crystallise when scratched but did not appear to be homogeneous. It was dissolved in pentane and

chromatographed on alumina (7·5 g.) prepared in pentane. Elution with pentane (20 c.c.) gave an oil (30 mg.) which solidified and was recrystallised from ether–methanol, to yield cholestane in plates, m. p. 79°, undepressed by admixture with cholestane. Further elution with pentane (3 × 20 c.c.) gave material which solidified only after many months and was found to crystallise readily from aqueous dioxan in plates (134 mg.), m. p. 61—65°; the identity of this hydrocarbon is being investigated. Further elution with benzene–pentane gave small quantities of oil which did not crystallise; these were united (28 mg.) and acetylated with acetic anhydride–pyridine at 20°. The material obtained by working up in the usual way was filtered in pentane through alumina; the resultant oil solidified on inoculation with 6β-acetoxycholestane, and the product was then sublimed in a molecular flask at 80—95°/0·01 mm., whereafter it readily crystallised from methanol in needles, m. p. 74°, which did not depress the m. p. of an authentic specimen of 6β-acetoxycholestane.

Cholestan-6α-ol (XII) *from* 3 : 5-cyclo*Cholestan-6α-ol* (IX).—3 : 5-*cyclo*Cholestane-6α-ol (158 mg.) was hydrogenated in presence of palladium oxide (92 mg.) in dioxan (10 c.c.) containing acetic acid (0·5 c.c.). After absorption of 1 mol. of hydrogen, the reduction was stopped, the catalyst removed, and the filtrate evaporated in a vacuum. The product was chromatographed in pentane on aluminium oxide (5 g.), 10 c.c. eluates being collected. Elution with pentane furnished cholestane and subsequently considerable quantities of oil which could not be induced to crystallise. Elution with benzene gave only traces of material, but ether yielded a solid (41 mg.), m. p. 115—123° which after repeated crystallisation from methanol furnished cholestan-6α-ol, m. p. 126—129°, undepressed by admixture with a genuine specimen.

Cholestane-3β : 6β-diol 6-Monoacetate (XVI).—Cholestane-3β : 6β-diol diacetate (2·5 g.) was heated under reflux with a solution of potassium hydroxide (6·25 g.) in methanol (1500 c.c.). The cold solution was then acidified with concentrated hydrochloric acid and the excess of acid neutralised with ammonia. After removal of methanol under reduced pressure, the residual oil was dried by azeotropic distillation with benzene and chromatographed on alumina (100 g.) prepared in pentane. Elution with benzene–pentane (1 : 4) (5 × 200 c.c.) gave an oil (1·13 g.) which by crystallisation from methanol gave cholestane-3β : 6β-diol 6-monoacetate in needles, m. p. 70°, with resolidification and remelting at 128° (cf. Plattner and Lang, *Helv. Chim. Acta*, 1944, **27**, 1872). Elution with benzene–pentane (1 : 1) (3 × 200 c.c.) gave a further quantity (0·68 g.) of the same monoacetate, whilst elution with chloroform gave cholestane-3β : 6β-diol (0·37 g.), m. p. 185—190°.

6β-*Acetoxycholestan-3-one* (XVII).—Cholestane-3β : 6β-diol 6-monoacetate (5·5 g.) in acetic acid (75 c.c.) was treated with 2% chromium trioxide–acetic acid (40 c.c.) and set aside for 15 hours at 25°. Excess of chromium trioxide was destroyed by addition of methanol, and the solvent removed under reduced pressure. The residual oil (5·03 g.) was extracted with ether and purified in the usual way; it crystallised from methanol in needles, m. p. 85—97°. The product was purified by chromatography on alumina (150 g.) prepared in pentane. Elution with benzene–pentane (1 : 1) and with benzene gave 6β-acetoxycholestan-3-one, which crystallised from methanol in needles, m. p. 100—101·5°.

6β-*Hydroxycholestan-3-one.*—6β-Acetoxycholestan-3-one (0·53 g.) was refluxed for 0·5 hour with 5% methanolic potassium hydroxide solution (50 c.c.). After addition of a little water and passage of excess of carbon dioxide, methanol was removed in a vacuum, water was added, and the product filtered off, to yield a solid (0·49 g.) which crystallised from acetone–methanol, to give 6β-hydroxycholestan-3-one as prisms, m. p. 181—184°, $[\alpha]_D$ +9°±2° (*c*, 0·542) (Marker and Krueger, *J. Amer. Chem. Soc.*, 1940, **62**, 79, give m. p. 190°).

Cholestan-6β-ol (X).—6β-Hydroxycholestan-3-one (158 mg.), hydrazine hydrate (0·2 c.c.), and a solution of potassium hydroxide (0·2 g.) in triethylene glycol (2·5 c.c.) was heated for 0·5 hour at 140—160° and then at 200° for 2 hours. The product was poured into water, the liquid acidified, the solution extracted with ether, and the ethereal extract purified in the usual way, to give an oil (85 mg.) which after 3 crystallisations from methanol gave prismatic needles, m. p. 79°, undepressed by admixture with authentic cholestan-6β-ol.

Cholestane-3β : 6β-diol (XV).—6β-Hydroxycholestan-3-one (51 mg.) in ether (5 c.c.) was added to lithium aluminium hydride (70 mg.) in ether (10 c.c.) and the reaction mixture left at 20° for 0·5 hour. Excess of lithium aluminium hydride was destroyed with 2N-sulphuric acid and the ethereal solution washed to neutrality with water, dried, and evaporated, to yield a solid (50 mg.), which after repeated crystallisation from acetone–methanol gave needles, m. p. 190—194°, undepressed by admixture with authentic cholestane-3β : 6β-diol.

Cholesta-2 : 6-diene (XIX).—Benzoylation of cholest-2-en-6β-ol (XVIII) (113 mg.) with benzoyl chloride (2 c.c.) in pyridine (4 c.c.) at 20° gave an oil which did not crystallise, even after

filtration of a solution in pentane through alumina. The oil, after being dried at 60°/0·05 mm. for 1 hour, was heated at 320°/10 mm. The residue was then distilled at 0·1 mm., the distillate extracted with pentane, and benzoic acid removed with 2N-sodium carbonate solution. The oil obtained by evaporation was chromatographed on alumina (3 g.) prepared in pentane. Elution with pentane (3 × 5 c.c.) gave an oil (22 mg.), which crystallised from ether–methanol and from methanol, to give cholesta-2 : 6-diene as long needles, m. p. 69—71°, $[\alpha]_D$ −1°±2° (*c*, 1·201) (Barton and Rosenfelder, *J.*, 1949, 2459, give m. p. 70—72°, $[\alpha]_D$ ±0°). Further elution with pentane and benzene–pentane gave small amounts of oil which failed to crystallise.

3 : 5-cyclo*Cholestane*.—3 : 5-*cyclo*Cholestan-6-one (0·58 g.) was heated under reflux for 0·5 hour with diethylene glycol (4·3 c.c.), hydrazine hydrate (0·43 c.c.), and sodium (0·6 g.) at 150° for 0·5 hour. The temperature was then allowed to rise to 195—200°, and refluxing continued for a further 2·5 hours. The cooled reaction mixture was diluted with water and extracted with pentane. The extract, after being washed with 2N-hydrochloric acid and with water, dried, and evaporated, gave an oil (0·59 g.) which was dried in a high vacuum and crystallised from acetone in needles, m. p. 74—75°. Filtration of a pentane solution through alumina gave 3 : 5-*cyclo*cholestane, m. p. 77—78°, $[\alpha]_D$ 80°±1° (*c*, 1·501) (Found, after drying at 60°/0·05 mm. for 6 hours : C, 87·3; H, 12·55. $C_{27}H_{46}$ requires C, 87·5; H, 12·5%).

*Acetolysis of Cholesteryl Toluene-*p*-sulphonate*.—Cholesteryl toluene-*p*-sulphonate (101 mg.) was heated under reflux with acetic acid (10 c.c.) for 36 hours under anhydrous conditions. Acetic acid was removed under reduced pressure, and the oily residue taken up in ether and washed successively with 2N-sodium carbonate and with water, dried, and evaporated. The resultant oil slowly crystallised and was chromatographed on alumina (4 g.) prepared in pentane; the column was eluted repeatedly with benzene–pentane (1 : 9; 10-c.c. fractions). Fractions 1—3 furnished a small amount of oil (13 mg.) which did not solidify on inoculation with *i*-cholesteryl acetate; this product consisted essentially of cholesteryl acetate since alkaline hydrolysis yielded slightly impure cholesterol, m. p. 143° after some softening. Eluates 6—15 furnished an oil (60 mg.) which solidified and by recrystallisation from ether–methanol gave plates, m. p. 103—112°, giving a positive test with tetranitromethane in chloroform; recrystallisation raised the m. p. to 111—114°, undepressed by admixture with authentic cholesteryl acetate.

Acetolysis of Cholesteryl Chloride.—(a) *With acetic anhydride and potassium acetate*. Cholesteryl chloride (5·13 g.) was heated with acetic anhydride (300 c.c.) (in which it is not very soluble) and anhydrous potassium acetate (7·5 g.) under reflux for 30 hours, whereupon the solution became deep brown. Acetic anhydride was removed under reduced pressure and the resulting oil purified in the usual manner. The product failed to crystallise and was hydrolysed with 5% ethanolic potassium hydroxide (250 c.c.) to give material which readily solidified. This was chromatographed on alumina (200 g.) prepared in pentane, and the chromatogram developed, eluates of 250 c.c. each being collected. Elution with pentane (fractions 3—7) gave a considerable amount of oil which solidified but proved difficult to recrystallise; this product gave a negative Beilstein test and was unsaturated, giving a yellow colour with tetranitromethane in chloroform, and appeared to contain cholesta-3 : 5-diene. Further elution with pentane yielded no significant amount of material, but use of benzene–pentane (1 : 4 and 1 : 1; 6 fractions) gave an oil (110 mg.) which crystallised partly on inoculation with 3 : 5-*cyclo*cholestanol; by treatment with hydriodic acid–acetic acid at 20° and subsequent chromatographic purification, with pentane as eluant, this material yielded cholesteryl iodide, m. p. 107°, and so must have consisted originally of 3 : 5-*cyclo*cholestanyl acetate, converted by hydrolysis into 3 : 5-*cyclo*cholestanol. Finally, the column was exhaustively eluted with ether, to yield a solid (3·43 g.), which crystallised from acetone in plates, m. p. 142—148° undepressed by admixture with cholesterol.

(b) *With acetic acid*. Cholesteryl chloride (200 mg.) was heated with acetic acid (20 c.c.) in a sealed tube at 95° for 72 hours; the reaction mixture was poured into water and the product isolated by repeated extraction with benzene. After hydrolysis with hot 5% ethanolic potassium hydroxide (25 c.c.) for 0·5 hour, the solvent was largely removed in a vacuum, and the product extracted with ether–benzene, to yield, after the usual purification, an oil (205 mg.) which crystallised. This material by chromatography on alumina (10 g.) and elution with pentane gave cholesteryl chloride, m. p. 93° (158 mg., 77·5%), and with ether gave cholesterol (43 mg.; calc. for 22·5% conversion, 43 mg.).

(c) *With acetic acid and silver acetate*. Cholesteryl chloride (500 mg.) and silver acetate (500 mg.) were dried separately at 50—60°/0·01 mm. for 30 minutes, and thereafter heated under reflux with acetic acid (30 c.c.) for 2·5 hours. The reaction mixture was concentrated in a vacuum to about one-quarter volume, diluted with water, and extracted with ether. The

product (528 mg.) was chromatographed on alumina (16 g.) prepared in pentane, with 40-c.c. eluates. Elution with pentane (fractions 1—3) gave 7 mg. of oil; further elution with pentane and pentane–benzene (fractions 4—17) gave cholesteryl acetate (473 mg.) which, recrystallised from acetone, had m. p. 112—114° (314 mg.). The material from the mother-liquors (147 mg.) and the oil (1·5 mg.) eluted from the column with benzene were combined and hydrolysed with methanolic potassium hydroxide, to give material (140 mg.), m. p. 144—148°, consisting of nearly pure cholesterol.

Action of Acetic Acid on 6β-*Methoxy*-3 : 5-cyclo*cholestane*.—6β-Methoxy-3 : 5-*cyclo*cholestane (m. p. 79°; 2·76 g.) was heated with acetic acid (50 c.c.) under reflux for 10 hours; on cooling, a crop of needles separated. Acetic acid was removed under reduced pressure and the residue taken up in ether, washed with 2N-sodium carbonate and with water, dried, and evaporated, to give an oil which solidified when dried at reduced pressure (wt., 2·9 g.). The product was chromatographed on alumina (100 g.) prepared in pentane and eluted with pentane, to furnish material, m. p. 89—101°, which from its behaviour on crystallisation was heterogeneous. The column was therefore washed with much ether and the eluates combined and evaporated. The residue was hydrolysed by boiling 3·3% methanolic potassium hydroxide for 1·5 hours; the product was worked up in the usual way to give a solid which was chromatographed on alumina (150 g.) prepared in pentane. Elution with pentane (10 × 200 c.c.) yielded an oil (156 mg.) which crystallised from acetone, to give a hydrocarbon as plates, m. p. 64—65°; this gave a yellow colour with tetranitromethane in chloroform and is being investigated. Elution with benzene–pentane, with benzene, and with ether failed to give any significant amount of material, but use of chloroform–ether gave cholesterol (2·50 g.) which separated from acetone in needles, m. p. 146—148° undepressed by admixture with a genuine specimen.

One of us (C. W. S.) acknowledges gratefully a grant from the Royal Society which has partly defrayed the expense of this work, whilst the other (G. H. R. S.) acknowledges the award of a Postgraduate Studentship by the University of Wales and a grant from the Department of Scientific and Industrial Research which enabled him to participate in this investigation. Microanalyses recorded are by Drs. Weiler and Strauss, Oxford.

UNIVERSITY COLLEGE, SWANSEA, UNIVERSITY OF WALES. [*Received, March 17th,* 1952.]

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648. *Steroids and Walden Inversion. Part VIII.* The Epimeric 6-Hydroxy-2 : 3-seco*cholestane*-2 : 3-dicarboxylic Acids.*

By C. W. SHOPPEE and G. H. R. SUMMERS.

The configurations at $C_{(6)}$ of the epimeric 6-hydroxy-2 : 3-*seco*cholestane-2 : 3-dicarboxylic acid 3→6-lactones have been established and these compounds have been related to the epimeric cholestan-6-ols, whereby the configurations of the latter are confirmed. The formation of 3→6-lactones is shown not to be by itself diagnostic of the configuration of steroid 6-hydroxyl groups.

IN connexion with work on the stereochemistry of the 3 : 5-*cyclo*steroid rearrangement,* we desired completely to establish the configurations of the epimeric cholestan-6-ols. Standard methods for the determination of configuration involve (i) molecular-rotation differences, (ii) steric-compression differences influencing (*a*) reaction rates and (*b*) equilibria, (iii) differences in molecular geometry influencing the facility of (*a*) ionic and (*b*) thermal elimination reactions, (iv) formation of cyclic compounds, and (v) fission of cyclic compounds. We have already utilised methods (i), (ii*a* and *b*), (iii*a* and *b*). An attempt to apply method (v) to the solution of our configurational problem was made incidentally by Plattner, Petrzilka, and Lang (*Helv. Chim. Acta*, 1944, **27**, 513); they examined the fission by catalytic reduction of 5α : 6α-epoxycholestane (Ruzicka, Furter, and Thomann, *ibid.*, 1933, **16**, 327) and obtained an inseparable mixture of cholestan-5α-ol and cholestan-6β-ol in which the presence of the latter could be established only by oxidation to cholestan-6-one. It seemed therefore of interest to examine method (iv).

Participation in lactone formation has enabled proof to be given of the β-configuration

* Part VII, preceding paper.

PLATE I.

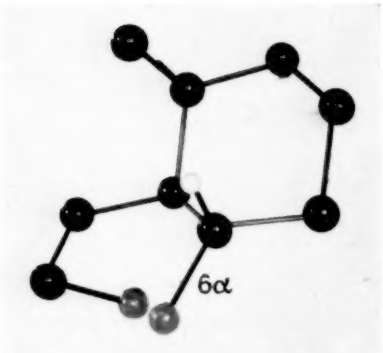
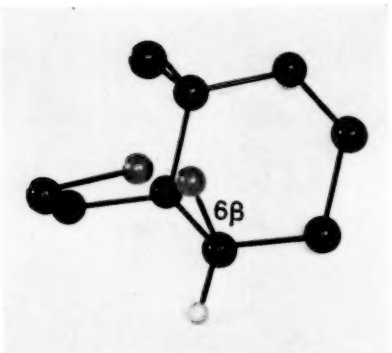


PLATE II.

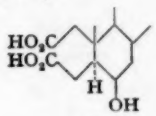


The white sphere represents the $C_{(6)}$-hydrogen atom, and the grey spheres represent the oxygen atoms of the hydroxyl groups attached to $C_{(6)}$ and of the carboxyl group attached to $C_{(3)}$.

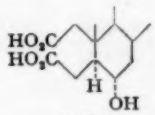
[*To face p.* 3375.

of $C_{(3)}$-hydroxyl group in cholesterol (Shoppee, *J.*, 1948, 1032), and of the α-configuration of the $C_{(12)}$-hydroxyl group in deoxycholic acid (Reichstein and Sorkin, *Helv. Chim. Acta*, 1946, **29**, 1218); we decided therefore to examine the capacity for 3→6-lactonisation of the epimeric 6-hydroxy-2 : 3-*seco*cholestane-2 : 3-dicarboxylic acids (I, II).

The literature already contains some evidence relating to analogous cases. Windaus (*Annalen*, 1926, **477**, 233) found that 6-keto-2 : 3-*seco*-5α-cholane-2 : 3 : 24-tricarboxylic acid (hyodeoxy*iso*bilianic acid, " oxo-Stadensäure ") by hydrogenation with platinum–acetic acid gives the 3→6β-lactonic acid and not the expected 6β-hydroxy-2 : 3-dicarboxylic acid, dehydration accompanying or immediately succeeding reduction, and that the 3→6β-lactonic acid is converted by treatment with sodium ethoxide at 190° for 10 hours into an isomeride. This is clearly the 6α→3-lactonic acid and arises by inversion of the $C_{(6)}$–O orientation from the β-configuration (polar) to the more thermodynamically stable α-configuration (equatorial).



(I)



(II)

Similarly the 3β : 6α-dihydroxysapogenin chlorogenin by oxidation furnishes 6-keto-2 : 3-*seco*-5α : 22α-spirostane-2 : 3-dicarboxylic acid (Noller, *J. Amer. Chem. Soc.*, 1937, **59**, 1092), which by hydrogenation with platinum–acetic acid gives directly the 3→6β-lactonic acid (Marker *et al.*, *ibid.*, 1947, **69**, 2183).

If ring B possesses the chair-conformation in the 6-hydroxy-acids (I, II), the $C_{(4)}$–$C_{(5)}$ bond has a fixed β-orientation but is capable of " free " rotation, so that the $C_{(3)}$–$C_{(4)}$ bond can traverse the surface of a cone of angle 120°. Examination of molecular models so constructed as to permit free rotation about the bond axes suggests that there should be little, if any, difference in the ease of formation of 3→6-lactonic acids with C–C and C–O bonds of normal length by the 6β- (I; Plate I *) and the 6α-hydroxy-acid (II; Plate II *). The following experimental evidence shows this to be the case, and that the formation of 6→3-lactones is not by itself diagnostic of the configuration of steroid 6-hydroxyl groups.

Windaus and Hossfeld (*Z. physiol. Chem.*, 1925, **145**, 175) by oxidation of the diacetate (VI) (m. p. 107°, $[\alpha]_D$ +39°) of cholestane-3β : 6α-diol (IX) (m. p. 217°, $[\alpha]_D$ +38°) with a concentrated solution of chromium trioxide in acetic acid at 95° obtained a small quantity of an acid, m. p. 196°. This acid gave a monomethyl ester, m. p. 99°, and titrated as a monobasic acid at 20° but as a dibasic acid at 95°; it was clearly a lactonic acid, and, as we shall show, it is the 3→6α-lactonic acid (III; R = H). We have repeated the work of Windaus and Hossfeld; in three repetitions, we obtained a small yield of the lactonic acid only once, the main oxidation product being a neutral substance, m.p. 223°. The production of the lactonic acid appears to depend on the presence of traces of water, and it may be noted that the oxidation of 3β : 6β-diacetoxy-5β-cholestane under similar drastic conditions leads to fission of the side-chain only with formation of 3β : 6β-diacetoxycholanic acid (Moffatt, *J.*, 1947, 812).

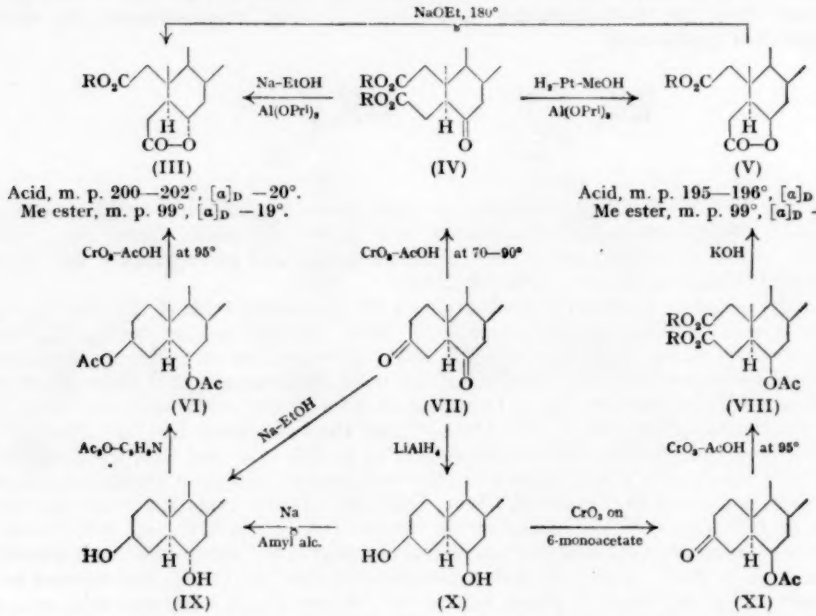
When 6-keto-2 : 3-*seco*cholestane-2 : 3-dicarboxylic acid (IV; R = H), obtained by oxidation of cholestane-3 : 6-dione (VII) (Windaus, *Ber.*, 1903, **36**, 3752), is reduced with sodium in ethanol + *iso*propyl alcohol, the 6α→3-lactonic acid, m. p. 202—204° (III; R = H) (methyl ester m. p. 99°, $[\alpha]_D$ −19°), of Windaus and Hossfeld is produced; the formation of the more thermodynamically stable 6α(equatorial)-configuration of the hydroxyl group in the precursor (II) of the lactonic acid by this reducing agent is to be expected.

If however the keto-dibasic acid (IV; R = H) is reduced catalytically by hydrogenation with platinum–ethanol or platinum–acetic acid (cf. Marker, Turner, and Ulshafer, *J. Amer. Chem. Soc.*, 1942, **64**, 1843) the isomeric 3→6β-lactonic acid, m. p. 195—196° (V; R = H), is formed; the reduction product, after esterification with diazomethane, by

* If ring B has the boat conformation, the acid (I) can readily form a 6β→3-lactonic acid, but the acid (II) cannot furnish a 6α→3-lactonic acid.

chromatographic analysis yielded the 3→6β-lactonic methyl ester (V; R = Me), m. p. 99°, $[\alpha]_D$ +59°. This ester, mixed with the isomeric 3→6α-lactonic methyl ester, m. p. 99°, in approximately equal proportion, gives a depression of ~12°; alkaline hydrolysis of the ester (V; R = Me) gives the 3→6β-lactonic acid (V; R = H).

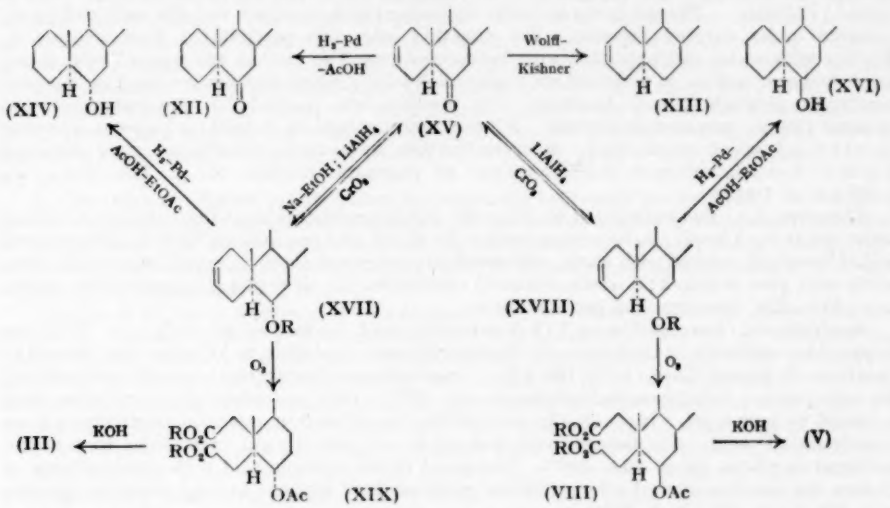
Reduction of the keto-dimethyl ester (IV; R = Me) with aluminium *iso*propoxide–*iso*propyl alcohol affords a mixture of the lactonic methyl esters (III and V; R = Me), partly separable by fractional crystallisation and completely separable by chromatography. Here lactonisation occurs by spontaneous elimination of a molecule of methanol, and may be compared with the ready 17→12-lactonisation of methyl 3α : 12α-dihydroxy-5β-androstane-17α-carboxylate (17-*isoætio*deoxycholic acid) (Sorkin and Reichstein, *loc. cit.*).



The 6β→3-lactonic acid (V; R = H) has also been obtained by partial synthesis. Reduction of cholestane-3 : 6-dione (VII) with lithium aluminium hydride gives cholestane-3β : 6β-diol (X) (m. p. 192°, $[\alpha]_D$ +13°), which by prolonged treatment with sodium–amyl alcohol at 180° undergoes partial conversion into the thermodynamically more stable cholestane-3β : 6α-diol (IX); the 3β : 6β-diol by acetylation gives the diacetate (m. p. 138°, $[\alpha]_D$ −23°), converted by partial hydrolysis into the 6β-monoacetate (Shoppee and Summers, *J.*, 1952, 1790) which by oxidation with chromium trioxide at 20° yields 6β-acetoxycholestan-3-one (XI). Further oxidation under more drastic conditions cleaves ring A, to afford 6β-acetoxy-2 : 3-*seco*cholestane-2 : 3-dicarboxylic acid, m. p. 238—240° (VIII; R = H), characterised as the dimethyl ester, m. p. 74—76°. Alkaline hydrolysis of the 6β-acetoxy-acid furnishes the 3→6β-lactonic acid (V; R = H).

A correlation of the lactonic acids (III and V; R = H) with the epimeric cholestan-6-ols, which confirms the configurations assigned to the latter, has been achieved in the following way. Cholest-2-en-6-one (XV), prepared by the method of Blunschy, Hardegger, and Simon (*Helv. Chim. Acta*, 1946, **29**, 199), was characterised by conversion into, and regeneration from, the dibromide, m. p. 132°, and its structure was confirmed by hydrogenation with palladium–acetic acid to cholestan-6-one (XII) and by Wolff–Kishner reduction to cholest-2-ene (XIII) (Fürst and Plattner, *ibid.*, 1949, **32**, 179; Barton and Rosenfelder, *J.*, 1949, 2359; 1951, 1048).

Reduction of cholest-2-en-6-one (XV) with lithium aluminium hydride gave a mixture of cholest-2-en-6α-ol (XVII; R = H), m. p. 138°, and cholest-2-en-6β-ol (XVIII; R = H), m. p. 90°, containing ~95% of the latter; the epimerides were separated chromatographically and both furnished cholest-2-en-6-one (XV) by mild oxidation with chromium



trioxide. Cholest-2-en-6β-ol (XVIII; R = H) was characterised as the dibromide, m. p. 146°, and was converted by hydrogenation with palladium–ethyl acetate–acetic acid into cholestan-6β-ol (XVI), m. p. 81°. Acetylation gave the acetate (XVIII; R = Ac), m. p. 75°, which by ozonolysis, followed by oxidation with chromium trioxide and esterification with diazomethane, gave the 6β-acetoxy-dimethyl ester (VIII; R = Me); this result provides further evidence of configuration at $C_{(6)}$ in cholestan-6β-ol (XVI).

Cholest-2-en-6α-ol (XVII; R = H) is formed in ~5% yield by reduction of cholest-2-en-6-one (XV) with lithium aluminium hydride, but by use of sodium in ethanol it becomes the sole product. It was converted by hydrogenation in the presence of palladium–ethyl acetate–acetic acid into cholestan-6α-ol (XIV), m. p. 129°. Acetylation yielded the acetate (XVII; R = Ac), m. p. 91—93°, which by ozonolysis, subsequent oxidation, and esterification with diazomethane gave the 6α-acetoxy-dimethyl ester (XIX; R = Me). This by alkaline hydrolysis furnished the 6α→3-lactonic acid (III; R = H), a result which confirms the configuration at $C_{(6)}$ assigned to cholestan-6α-ol (XIV) and, by exclusion, that assigned to cholestan-6β-ol (XVI).

Lastly, the direct conversion of the less thermodynamically stable 3→6β-lactonic acid (V) into the more thermodynamically stable 3→6α-lactonic acid (III) by treatment with sodium ethoxide at 180° supplies final confirmation of the correctness of the configurations assigned at $C_{(6)}$.

Experimental

The general notes on p. 3369 apply also to this paper.

6-Keto-2 : 3-secocholestan-2 : 3-dicarboxylic Acid (IV).—This was prepared from cholestane-3 : 6-dione by a modification of the methods described by Windaus (*Ber.*, 1903, **36**, 3752) and Marker (*J. Amer. Chem. Soc.*, 1942, **64**, 1843). A solution of cholestane-3 : 6-dione (m. p. 170—173°; 80 g.) in glacial acetic acid (1600 c.c. distilled over CrO_3) was heated to 65—70° and treated with an aqueous solution of chromium trioxide (64 g. in 80 c.c. of water) added dropwise to the vigorously stirred solution during 0·5 hour. Depending on the rate of addition of the chromic acid, the reaction temperature increased but was not allowed to exceed 95°. After 2 hours the reaction mixture was diluted with hot water (1000 c.c.) and left overnight. The reaction product was filtered off, washed with water, and dried on porous porcelain.

Unchanged starting material (37 g.) was removed by heating the product with a 10% aqueous potassium hydroxide (300 c.c.) for 0·5 hour, followed by filtration of the insoluble cholestane-3 : 6-dione. The alkaline filtrate, after cooling in ice, gave by treatment with 4N-sulphuric acid a voluminous precipitate of 6-keto-2 : 3-*seco*cholestane-2 : 3-dicarboxylic acid. The acid was converted into its dimethyl ester by methanol (500 c.c.) and concentrated sulphuric acid (50 c.c.) (2 hours). The sulphuric acid was neutralised with ammonia and the methanol partly removed under reduced pressure. The dimethyl ester was precipitated from solution by dilution with water and extracted with benzene–ether. The extract was washed with water, dried, and evaporated, to yield a thick brown oil (14·3 g.), which was further dried by repeated azeotropic distillation with benzene. The product was purified by chromatography on alumina (700 g.) prepared in pentane. Elution with pentane (5 × 1000 c.c.) gave a colourless oil (11·7 g.) which crystallised. Recrystallisation from acetone–methanol gave dimethyl 6-keto-2 : 3-*seco*cholestane-2 : 3-dicarboxylate as prismatic needles, m. p. 113—114°, $[\alpha]_D$ +20°±1° (*c*, 1·829).

The ester (3 g.) was hydrolysed by ethanolic potassium hydroxide (100 c.c. of 10% solution) under reflux for 1 hour. After concentration the diacid was precipitated at 0° by 4N-sulphuric acid, filtered off, washed with water, and dried on porous porcelain. Crystallisation from 60% acetic acid gave 6-keto-2 : 3-*seco*cholestane-2 : 3-dicarboxylic acid (2·6 g.) as glistening plates, m. p. 219—220° (decomp. and gas evolution).

6α-*Hydroxy*-2 : 3-seco*cholestane*-2 : 3-*dicarboxylic Acid* 3→6α-*Lactone* (III).—(*a*) This was prepared by oxidation of cholestane-3β : 6α-diol diacetate according to Windaus and Hossfeld's directions (*Z. physiol. Chem.*, 1925, **145**, 175). Once in three attempts was a lactonic acid isolated, the main product being a neutral substance, m. p. 223°, which was difficult to recrystallise since it tended to form a gel. It eventually recrystallised in plates from methanol containing a trace of hydrochloric acid. The lactonic acid, isolated in very small yield, crystallised from ether–methanol in plates, m. p. 200—202°. Treatment of the lactonic acid with diazomethane at 0° gave the lactonic methyl ester, which crystallised from pentane in long prismatic needles, m. p. 99°, $[\alpha]_D$ −19°±1° (*c*, 2·61).

(*b*) 6-Keto-2 : 3-*seco*cholestane-2 : 3-dicarboxylic acid (2·6 g.) in *iso*propyl alcohol (200 c.c.) was treated with sodium (5 g.). The sodium salt of the above acid separated immediately, ethanol (200 c.c.) was added, and the mixture refluxed with sodium (5·3 g.) for 2 hours. The solution, on concentration, dilution with water, and acidification with 4N-sulphuric acid, gave a brown semi-solid precipitate which solidified on cooling. The reaction product was taken up in ether and the ethereal extract washed with water, dried, and evaporated, to yield a solid which crystallised from ether–methanol in plates, m. p. 200—202°, $[\alpha]_D$ −20°±2° (*c*, 1·847) (yield, after three crystallisations : 1·95 g.). The lactonic acid so obtained did not depress the m. p. of that prepared by the method of Windaus and Hossfeld (*loc. cit.*). Titration with 0·01N-potassium hydroxide at 20° confirmed the monobasic nature of the compound [Found : *M*, 437. Calc. for $C_{27}H_{44}O_4$: *M* (monobasic), 432·6].

6β-*Hydroxy*-2 : 3-seco*cholestane*-2 : 3-*dicarboxylic Acid* 6β→3-*Lactone* (V).—6-Keto-2 : 3-*seco*cholestane-2 : 3-dicarboxylic acid (500 mg.) in absolute ethanol (110 c.c.) was hydrogenated in the presence of platinum oxide (200 mg.). The catalyst was reduced immediately but the hydrogenation proceeded very slowly, one mol. of hydrogen being absorbed only after 8 hours. The catalyst was filtered off and the solution evaporated to dryness. The white solid lactonic acid obtained was converted with ethereal diazomethane into its methyl ester, which was purified by chromatography on alumina (20 g.) prepared in pentane. Elution with pentane (50-c.c. eluates : fractions 1—5) yielded a colourless oil which crystallised from methanol in needles, to give *methyl* 6β-*hydroxy*-2 : 3-seco*cholestane*-2 : 3-*dicarboxylate* 3→6β-*lactone*, m. p. 99—100°, $[\alpha]_D$ +59°±2° (*c*, 0·886) (Found, after drying at 70°/0·02 mm. for 1 hour : C, 75·7; H, 10·5. $C_{28}H_{46}O_4$ requires C, 75·3; H, 10·4%). Further pentane eluates (fractions 6 and 7) gave oils which could not be induced to crystallise, but which by rechromatography were resolved into the above 3→6β-lactonic ester and a little dimethyl 6-keto-2 : 3-*seco*cholestane-2 : 3-dicarboxylate (IV; R = Me). A mixture of the 3→6β-lactonic methyl ester, m. p. 99°, with the 3→6α-lactonic methyl ester, m. p. 99°, melted at 88°.

Hydrolysis of the 3→6β-lactonic methyl ester, with a dioxan–methanolic solution of potassium hydroxide gave the lactonic acid (V), which crystallised from methanol in needles, m. p. 195—196°, $[\alpha]_D$ +58·5°±2° (*c*, 1·95).

6β-*Acetoxy*-2 : 3-seco*cholestane*-2 : 3-*dicarboxylic Acid* (VIII).—A solution of 6β-acetoxycholestan-3-one (m. p. 101°; 3·2 g.) in 90% acetic acid (90 c.c.) was treated at 60—65° with chromium trioxide (3 g.) in 90% acetic acid (30 c.c.) added dropwise during 0·5 hour to the

stirred solution. Stirring was continued for 1 hour; excess of chromium trioxide was then destroyed by addition of methanol (20 c.c.), and the solvent removed under reduced pressure. The green sludge obtained was dissolved in ether, the ethereal extract washed until colourless with 2N-sulphuric acid, to neutrality with water, and dried, and the ether evaporated, to yield an oil. This was extracted with three portions of hot 2N-sodium carbonate solution, and the extracts were filtered. The combined alkaline filtrates by acidification yielded a white precipitate, which was filtered off, dissolved in ether, and purified in the usual way. The oil obtained crystallised when rubbed with acetic acid and on recrystallisation from acetic acid gave 6β-acetoxy-2 : 3-*seco*cholestane-2 : 3-dicarboxylic acid (0·7 g.), m. p. 238—240°. Treatment with ethereal diazomethane at 0° for 0·25 hour yielded after purification a *dimethyl* ester, which crystallised from methanol as needles, m. p. 74—76° (Found, after drying at 40°/0·02 mm. for 3 hours and 20°/0·02 mm. for 5 hours: C, 71·3; H, 10·35. $C_{31}H_{52}O_6$ requires C, 71·5; H, 10·1%).

Hydrolysis was effected by 5% ethanolic potassium hydroxide for 0·5 hour. Acidification gave a white precipitate which was filtered off; it was readily soluble in ether and the solution by evaporation gave an oil which crystallised spontaneously and yielded needles, m. p. 195°, from methanol, undepressed by admixture with 6β-hydroxy-2 : 3-*seco*cholestane-2 : 3-dicarboxylic acid 3→6β-lactone (V).

Formation of the 3→6β- *and* 3→6α-*Lactonic Methyl Esters by Use of Aluminium* iso-*Propoxide*.—Methyl 6-keto-2 : 3-*seco*cholestane-2 : 3-dicarboxylate (5·3 g.) in absolute *iso*propyl alcohol (30 c.c.) was treated with aluminium *iso*propoxide (4 g.). The reduction as indicated by acetone formed and distilled off required 4 hours for completion. *iso*Propyl alcohol was removed under reduced pressure, the residual oil, after treatment with water and ice-cold 2N-sulphuric acid, was extracted with ether, and the extract worked up in the usual manner, to yield a colourless oil. This crystallised when rubbed with methanol, and recrystallisation from the same solvent gave thin needles, m. p. 95—99°, which on recrystallisation from pentane yielded even thinner needles, m. p. 99° (3·4 g.) undepressed on admixture with methyl 6β-hydroxy-2 : 3-*seco*cholestane-2 : 3-dicarboxylate 3→6β-lactone (V; R = Me). The mother-liquors from these crystallisations by evaporation gave an oil (2 g.), which was chromatographed on neutral alumina (80 g.) prepared in pentane, with pentane elution (100-c.c. fractions). The product (1·1 g.), m. p. 99° (from methanol), from fractions 6—9 consisted of the 3→6β-lactonic methyl ester (V; R = Me) and showed no m. p. depression when mixed with a genuine specimen. The product (0·7 g.), m. p. 98—99°, from fractions 12—15 consisted of the 6α→3-lactonic methyl ester (III; R = Me) and gave no m. p. depression by admixture with this. The material (0·29 g.; m. p. 81—92°) from fractions 10 and 11 consisted of a mixture of the isomeric lactonic methyl esters.

Alkaline hydrolysis of the pure lactonic esters furnished the respective lactonic acids (III, V; R = H), which by treatment with ethereal diazomethane regenerated the respective lactonic esters.

Conversion of the 3→6β-*Lactonic Acid* (V) *into the* 3→6α-*Lactonic Acid* (III).—6β-Hydroxy-2 : 3-*seco*cholestane-2 : 3-dicarboxylic acid 3→6β-lactone (m. p. 195—196°; 547 mg.) was heated at 189—200° for 15 hours with a solution of sodium (0·5 g.) in absolute ethanol (5 c.c.). The reaction product was separated by precipitation from dilute aqueous-alcoholic solution with 2N-sulphuric acid, and crystallisation from methanol gave plates, m. p. 200—202°, which showed no depression on admixture with 6α-hydroxy-2 : 3-*seco*cholestane-2 : 3-dicarboxylic acid 3→6α-lactone.

Cholest-2-en-6-one (XV).—This was prepared by the method of Blunschy, Hardegger, and Simon (*Helv. Chim. Acta*, 1946, **29**, 199); it had m. p. 104—105°, and was characterised as the dibromide, prepared in chloroform: the oil (55 mg.) obtained crystallised from acetone–methanol, to give 2 : 3-*dibromocholestan*-6-*one* in fine needles, m. p. 132°, $[\alpha]_D$ +48°±1° (*c*, 0·737) (Found, after drying at 20°/0·01 mm. for 20 hours: C, 59·4; H, 8·1. $C_{27}H_{44}OBr_2$ required C, 59·65; H, 8·0%). Treatment of the dibromide with zinc dust in acetic acid followed by the usual purification regenerated cholest-2-en-6-one, m. p. 102°. Its structure was confirmed as follows: (*a*) Cholest-2-en-6-one (515 mg.) in triethylene glycol (7 c.c.) was heated at 150° with potassium hydroxide (0·5 g.) and pure hydrazine hydrate (3 c.c.) for 0·5 hour and then at 220° for a further 2·5 hours. The reaction mixture, after cooling, was poured into water and extracted with pentane (50 c.c.), and the extract washed with water, dried, and evaporated. The oil so obtained was purified by filtration of its solution in pentane through alumina, to give cholest-2-ene (369 mg.), which crystallised from ether–methanol in needles, m. p. 74°. (*b*) Cholest-2-en-6-one (90 mg.) was hydrogenated in acetic acid (5 c.c.) in the presence of palladium oxide (30 mg.).

After the theoretical uptake of hydrogen the solution was filtered and evaporated, to yield an oil which was purified in the usual manner. The oil (80 mg.) crystallised from methanol in plates, m. p. 98°, giving no depression with genuine cholestan-6-one.

Cholest-2-en-6α- (XVII) *and -6β-ol* (XVIII).—Cholest-2-en-6-one (m. p. 104—105°; 3·7 g.) in ether (200 c.c.) was heated under reflux for 0·5 hour with finely powdered lithium aluminium hydride (1·0 g.). The mixture was cooled in ice and excess of lithium aluminium hydride destroyed with ice-water and 4N-sulphuric acid. The ethereal solution, worked up in the usual manner, yielded an oil (3·5 g.) which was dried by repeated evaporation with benzene under reduced pressure and chromatographed on alumina (120 g.) prepared in pentane; 200-c.c. eluates were collected. The substance (3·1 g.) from fractions 9—17 (eluant, 1 : 4→1 : 1 benzene–pentane), crystallised from acetone–methanol, had m. p. 89—90°, $[\alpha]_D$ +39·5°±2° (*c*, 4·01), +43°±2° (*c*, 1·193) and proved to be *cholest-2-en-6β-ol* (XVIII) (Found, after sublimation at 90°/0·05 mm.: C, 83·95; H, 11·9. $C_{27}H_{46}O$ requires C, 83·8; H, 12·0%), characterised as the *dibromide* (prepared in chloroform), needles (from acetone–methanol), m. p. 146°, $[\alpha]_D$ +64°±1° (*c*, 1·891) (Found, after drying at 60°/0·01 mm. for 2 hours: C, 59·2; H, 7·9. $C_{27}H_{46}OBr_2$ requires C, 59·3; H, 8·4%). The alcohol was converted into the *acetate* (acetic anhydride–pyridine at 20°), prisms (from aqueous acetone), m. p. 75°, $[\alpha]_D$ +19·5°±1° (*c*, 1·767) (Found, after drying at 40°/0·01 mm. for 6 hours: C, 81·3; H, 11·3. $C_{29}H_{48}O_2$ requires C, 81·2; H, 11·3%). By oxidation with 2% chromium trioxide–acetic acid (0·5 c.c.) at 20°, cholest-2-en-6β-ol (24 mg.) yielded cholest-2-en-6-one (21 mg.) as needles (from acetone), m. p. 102—104°, undepressed by admixture with a genuine specimen.

The compound (0·11 g.) from fractions 20 and 21 (eluant, 1 : 1 benzene–pentane) crystallised from pentane in prisms, m. p. 138°, $[\alpha]_D$ +72°±4° (*c*, 2·915); it was the minor reduction product, *cholest-2-en-6α-ol* (XVII) (Found, after drying at 40°/0·01 mm. for 6 hours: C, 83·8; H, 11·5%); it gave an oily acetate (see below). By oxidation with chromium trioxide at 20°, it gave cholest-2-en-6-one, m. p. 102—104°.

Cholest-2-en-6α-ol (XVII).—This substance was more satisfactorily prepared as follows: Cholest-2-en-6-one (XV) (133 mg.) in boiling ethanol (5 c.c.) was treated with sodium (*ca.* 0·5 g.). The cold reaction mixture was diluted with water and the greater part of the ethanol removed under reduced pressure; working up in the usual way gave a product which was treated in pyridine (1·5 c.c.) with acetic anhydride (1·0 c.c.) at 15° for 12 hours. The resultant oil was filtered in pentane through alumina (4 g.) prepared in pentane; evaporation of the filtrate gave an oil which crystallised partly on standing and completely when moistened with methanol. *Cholest-2-en-6α-yl acetate* (XVII; R = Ac) was obtained by recrystallisation from acetone–methanol as prismatic needles, m. p. 91—93°, $[\alpha]_D$ +105°±3° (*c*, 1·200) (Found, after drying at 80°/0·02 mm. for 1 hour: C, 81·3; H, 11·3%).

Cholestan-6α-ol (XIV).—Cholest-2-en-6α-ol (50 mg.) was hydrogenated with palladium oxide (50 mg.) in acetic acid–ethyl acetate (1 : 1; 30 c.c.). After removal of the catalyst, complete evaporation of the filtrate in a vacuum gave a solid, which by crystallisation from acetone yielded cholestan-6α-ol in plates, m. p. 128—129°.

Cholestan-6β-ol (XVI).—Cholest-2-en-6β-ol (150 mg.) was hydrogenated as above. The oil obtained tended to crystallise from methanol but the crystals did not appear to be homogeneous. After being dried by azeotropic distillation with benzene, the oil (141 mg.) was chromatographed on alumina (5 g.) prepared in pentane. Elution with pentane (7 × 15 c.c.) gave cholestane, m. p. 78—80° (33 mg.), and subsequent elution with ether furnished an oil (96 mg.) which gave no colour with tetranitromethane in chloroform and on inoculation with authentic cholestan-6β-ol crystallised immediately in prisms, m. p. 75—80°. Further recrystallisation from methanol gave cholestan-6β-ol, m. p. 80—81°.

Ozonolysis of Cholest-2-en-6β-yl Acetate.—Cholest-2-en-6β-yl acetate (250 mg.) in glacial acetic acid (10 c.c.) was treated with ozonised oxygen for 0·5 hour. The solution was then diluted with water (2 c.c.) and warmed on a steam-bath for 2 hours. To the cold (0°) mixture, chromium trioxide (5 c.c. of a 1% solution in acetic acid) was added and the whole left overnight. Excess of chromic acid was destroyed with methanol, and the solution evaporated completely in a vacuum. The residue (114 mg.) was dissolved in ether, and the solution washed with ice-cold N-sulphuric acid, and with water, dried and evaporated. Ethereal diazomethane was added and the mixture left at 0° for 0·5 hour; an oil was isolated in the usual way which crystallised from methanol in needles, m. p. 73—76°, and was identical with dimethyl 6β-acetoxy-2 : 3-*seco*cholestane-2 : 3-dicarboxylate (VIII).

Ozonolysis of Cholest-2-en-6α-yl Acetate.—This acetate (450 mg.) similarly gave dimethyl 6α-acetoxy-2 : 3-*seco*cholestane-2 : 3-dicarboxylate (XIX) which did not crystallise. A portion

was hydrolysed with hot 4% methanolic potassium hydroxide for 0·5 hour to 6α-hydroxy-2 : 3-*seco*cholestane-2 : 3-dicarboxylic acid 3→6α-lactone, plates, m. p. 200—202° (from ether–methanol), which did not depress the m. p. of a genuine specimen and furnished by treatment with ethereal diazomethane the methyl ester, m. p. 99°.

Conversion of Cholestane-3β : 6β-diol (X) *into Cholestane-3β : 6α-diol* (IX).—Cholestane-3β : 6β-diol (1 g.) was heated with sodium (1 g.) and amyl alcohol (10 c.c.) in a sealed tube at 200° for 40 hours. After cooling, the solution was poured into excess of 2N-hydrochloric acid and extracted with ether. The ethereal extract was washed with water and saturated sodium carbonate solution, dried, and evaporated, to give a dark brown solid. This was acetylated with acetic anhydride and worked up in the usual way, to give an oil (617 mg.), which was chromatographed on alumina (25 g.) prepared in pentane and repeatedly eluted with pentane (150 c.c.). Fractions 1—3 gave an oil which crystallised from methanol and had m. p. 138° undepressed on admixture with authentic cholestane-3β : 6β-diol diacetate. Fractions 4 and 5 could not be crystallised, but fractions 6—8 by inoculation with cholestane-3β : 6α-diol diacetate gave a solid, m. p. 85—101°. Alkaline hydrolysis of these last fractions yielded a solid which crystallised from acetone in plates, m. p. 200—211°, which gave no depression with genuine cholestane-3β : 6α-diol, m. p. 217°.

One of us (C. W. S.) acknowledges gratefully a grant from the Royal Society which has partly defrayed the expense of this work, whilst the other (G. H. R. S.) acknowledges the award of a Postgraduate Studentship by the University of Wales and a grant from the Department of Scientific and Industrial Research. Microanalyses are by Dr. Weiler and Dr. Strauss, Oxford.

UNIVERSITY COLLEGE, SWANSEA.
UNIVERSITY OF WALES. [*Received, March 17th,* 1952.]

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649. *The Possible Occurrence of Geometrical Isomerism Among the Diazosulphones.*

By H. C. FREEMAN, R. J. W. LE FÈVRE, (MISS) J. NORTHCOTT, and (MISS) I. YOUHOTSKY.

The dipole moments and spectra of $C_6H_5{\cdot}N{:}N{\cdot}SO_2{\cdot}C_6H_5$ and five of its derivatives have been examined. The azo-group appears to be *trans* in the known forms, although irradiation of their solutions in benzene or alcohol provides signs that beneath an irreversible photo-decomposition some reversible change may be occurring.

DESPITE the fact that all diazo-compounds of the general formula $Ar{\cdot}N{:}N{\cdot}X$ should—on Hantzsch's configurational view of the $-N{:}N-$ group—be capable of existence in *cis*- and *trans*-forms, many are recorded in the literature which have never been so separated. Accordingly, examples where $X = CO{\cdot}NH_2$ and NMe_2 were recently reinvestigated and observations were noted (Freeman, Le Fèvre, and Wilson, *J.*, 1951, 1977; Le Fèvre and Liddicoet, *J.*, 1951, 2743) of a kind reconcilable with classical prediction (cf. *Ber.*, 1894, **27**, 1702). The present paper continues this programme with the diazosulphones $R{\cdot}N{:}N{\cdot}SO_2{\cdot}R'$. These substances, although formed directly from sulphinic acids and diazonium salts, were recognised by their discoverer, Koenigs (*Ber.*, 1877, **10**, 1531), as sulphones, and not sulphinates $R{\cdot}N{:}N{\cdot}O{\cdot}SO{\cdot}R$, by the reaction :

$$Ph{\cdot}N_2X + Ph{\cdot}SO_2H \longrightarrow Ph{\cdot}N{:}N{\cdot}SO_2Ph$$

$$Ph{\cdot}SO_2Cl + Ph{\cdot}NH{\cdot}NH_2 \xrightarrow{H_2\downarrow\ \uparrow HgO} Ph{\cdot}NH{\cdot}NH{\cdot}SO_2Ph$$

Unsuccessful searches among the diazosulphones for geometrical isomerism have been reported by von Pechmann (*Ber.*, 1895, **28**, 861) and Hantzsch and Singer (*ibid.*, 1897, **30**, 312), while Hantzsch and Glogauer (*ibid.*, p. 2557) found that certain pairs of "*n*-" and "*iso*-"diazocyanides were chemicallly transformable into *single* diazosulphones. It should be mentioned, for completeness, that Claasz (*ibid.*, 1911, **44**, 1415) has claimed the isolation of an authentic diazonium sulphinate, having salt-like properties and differing in other respects from the diazosulphones handled by us.

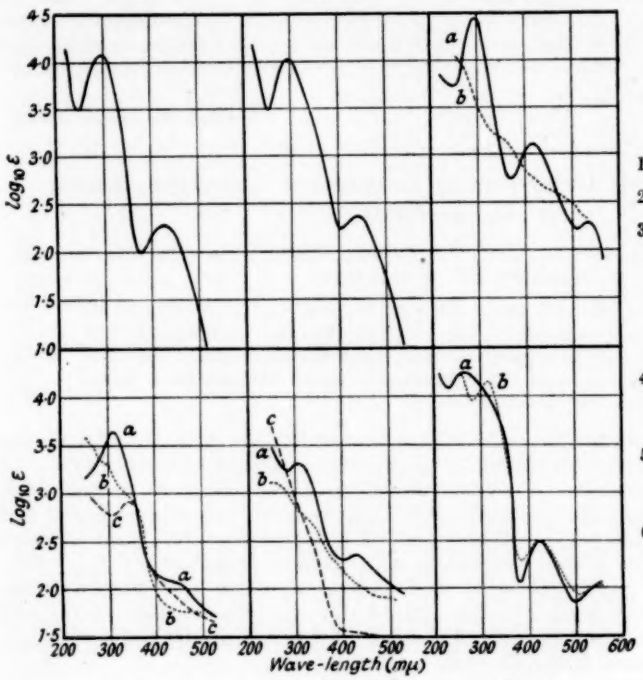
Present Work.—This concerns six phenyldiazosulphones, prepared by methods described by Hantzsch or von Pechmann in the following papers: *Ber.*, 1895, **28**, 862; 1897, **30**, 312; 1898, **31**, 641. The m. p.s and appearances of the specimens used are listed:

R in $R{\cdot}N_2{\cdot}SO_2{\cdot}C_6H_5$		M. p.
C_6H_5	Orange rhombs from EtOH	78° (lit., 78°)
o-$Cl{\cdot}C_6H_4$ *	Orange flakes from EtOH	98° (new)
p-$Cl{\cdot}C_6H_4$	Yellow needles from EtOH	107° (lit., 106°)
p-$Br{\cdot}C_6H_4$	Bronze needles from EtOH	115° (lit., 116°)
p-$NO_2{\cdot}C_6H_4$	Red prisms from $CHCl_3$	136° lit., 136°)
2 : 4 : 6-$C_6H_2Br_3$	Yellow-orange powder, pptd. from Et_2O by absolute EtOH	121° (decomp.)

* Found: N, 9·9. $C_{12}H_9N_2O_2SCl$ requires N, 10·0%.

These (with one exception) have been examined by applying to them procedures previously used by Le Fèvre *et al.* on other azo- (*J.*, 1939, 531, 1595; *J.*, 1951, 1814) and diazo-derivatives (*J.*, 1949, 33, 1106; 1950, 3128; 1951, 415, and *locc. cit.*): solutions, made

FIG. 1. FIG. 2. FIG. 3.



Diazosulphones

1. $C_6H_5{\cdot}N_2{\cdot}SO_2Ph$
2. *o*-$Cl{\cdot}C_6H_4{\cdot}N_2{\cdot}SO_2Ph$
3. *p*-$Cl{\cdot}C_6H_4{\cdot}N_2{\cdot}SO_2Ph$
   (*a*) Initial; (*b*) irradiated.
4. *p*-$Br{\cdot}C_6H_4{\cdot}N_2{\cdot}SO_2Ph$
   (*a*) Initial; (*b*) irradiated; (*c*) final.
5. 2 : 4 : 6-$C_6H_2Br_3{\cdot}N_2{\cdot}SO_2Ph$
   (*a*) Initial; (*b*) irradiated; (*c*) final.
6. *p*-$NO_2{\cdot}C_6H_4{\cdot}N_2{\cdot}SO_2Ph$
   (*a*) Initial; (*b*) irradiated.

FIG. 4. FIG. 5. FIG. 6.

up in the absence of daylight in opaque flasks, were submitted to dielectric-constant, density, and spectrographic-absorption measurements, benzene being the solvent for the first two observations, and alcohol for the third. Next, the same solutions were transferred to clear-glass containers and exposed to direct sunlight for 1—2 hours, and the measurements at once repeated. Finally, the solutions were stored in the dark for two days, after which measurements were made a third time.

Apparatus and techniques have been described in the references just quoted (cf. also Calderbank and Le Fèvre, *J.*, 1948, 1949); symbols are as defined by Le Fèvre * (*Trans.*

* Except that subscripts 1 and 2 are now used to denote solvent and solute respectively (cf. Buckingham and Le Fèvre, *J.*, 1952, 1932).

Faraday Soc., 1950, **46**, 1). The spectra were recorded on a Beckman photoelectric spectrophotometer, Model D.U.; they are reproduced as in the figures. Table 1 contains the dielectric-constant and density data from which the apparent dipole moments of the solutes before irradiation can be estimated. This is done in Table 2, the polarisations ($_\infty P_2$) at infinite dilution being derived *via* the equation $_\infty P_2 = M_2[p_1(1 - \beta) + C\alpha\varepsilon_1]$, where $p_1 = 0{\cdot}34086$ or $0{\cdot}34161$ c.c. and $C = 0{\cdot}18809$ or $0{\cdot}19039$ for benzene at 25° or 30°, respectively. The mean quantities $\alpha\varepsilon_1$ and βd_1 have been obtained as $\Sigma(\varepsilon_{12} - \varepsilon_1)/\Sigma w_1$ and $\Sigma(d_{12} - d_1)/\Sigma w_2$. The refractivities under $[R_L]_D$ have been calculated by assuming that $R_{N_2} = 9$ c.c. (Anderson, Le Fèvre, and Wilson, *J.*, 1949, 2082) and $R_{C_6H_5} = 25{\cdot}4$, $R_{SO_2} = 7{\cdot}8$ (as in sulphates), $R_{Cl} = 5{\cdot}8$, $R_{Br} = 8{\cdot}9$, and $R_{NO_2} = 6{\cdot}71$ (Vogel, *J.*, 1948, 1833). The following actual determination on the *p*-chloro-compound in benzene was made as a check :

10^6w_2	d_4^{25}	n_D^{25}	$[R_L]_D$, c.c.	10^6w_2	d_4^{25}	n_D^{25}	$[R_L]_D$, c.c.
0	0·87378	1·4972	—	20,680	0·87962	1·4984	72·9

Table 3 summarises the details of the curves shown in Figs. 1—6.

TABLE 1.*

Benzenediazophenylsulphone at 25°					p-*Chlorobenzenediazophenylsulphone at 25°*				
10^6w_2	2276	2281	3681	4059	10^6w_2	5064	8341	9637	10,941
ε^{25}	2·2916	2·2910	$2{\cdot}3019_5$	2·3054	ε^{25} (Inl.)	2·3100	2·3335	2·3452	2·3540
d_4^{25}	0·87448	$0{\cdot}87447_5$	0·87492	0·87503	d_4^{25} (Inl.)	0·87517	0·87611	0·87642	0·87680

p-*Chlorobenzenediazophenylsulphone at 30°* †					p-*Bromobenzenediazophenylsulphone at 30°*			
10^6w_2	842	1717	2820	4796	10^6w_2	263	378	962
ε^{30} (Inl.)	2·2691	2·2774	2·2825	—	ε^{30} (Inl.)	2·2639	2·2650	2·2700
ε^{30} (Irr.)	2·286	2·293	2·299	—	ε^{30} (Irr.)	—	2·278	2·288
ε^{30} (Fin.)	Decomposition evident				ε^{30} (Fin.)	—	2·272	2·274
d_4^{30} (Inl.)	0·86739	0·86780	—	0·86892	d_4^{30} (Inl.)	0·86728	0·86739	0·86751

p-*Nitrobenzenediazophenylsulphone at 25°*					2 : 4 : 6-*Tribromobenzenediazophenylsulphone at 30°*			
10^6w_2	868	2211	3519	4685	10^6w_2	2159	4199	8260
ε^{25} (Inl.)	2·2815	2·2918	2·3031	2·3132	ε^{30} (Inl.)	2·2726	2·2864	2·3033
ε^{25} (Irr.)	$2{\cdot}279_5$	—	$2{\cdot}292_5$	2·303	ε^{30} (Irr.)	2·289	2·325	2·365
ε^{25} (Fin.)	2·280	—	2·302	2·313	ε^{30} (Fin.)	2·273	2·284	2·313
d_4^{25} (Inl.)	0·87409	0·87450	0·87549	0·87547	d_4^{30} (Inl.)	0·86813	0·87008	0·87217

* Solvent = benzene. For $10^6w_2 = 0$, $\varepsilon^{25} = 2{\cdot}2725$, $\varepsilon^{30} = 2{\cdot}2628$, $d_4^{25} = 0{\cdot}87378$, $d_4^{30} = 0{\cdot}86718$.
† Inl. = initial; Irr. = irradiated; Fin. = final.

TABLE 2.

Solute	M_2	Mean $\alpha\varepsilon_1$	Mean β	$_\infty P_1$, c.c.	$[R_L]_D$, c.c.	μ,* D
$Ph{\cdot}N_2{\cdot}SO_2Ph$	246	8·12	0·352	430	68	$4{\cdot}2_0$
p-$Cl{\cdot}C_6H_4{\cdot}N_2{\cdot}SO_2Ph$	281	7·55 7·44	0·403 0·316	461 459	73	$4{\cdot}3_0$ $4{\cdot}3_1$
p-$Br{\cdot}C_6H_4{\cdot}N_2{\cdot}SO_2Ph$	325	6·55	0·460	465	76	$4{\cdot}4_0$
p-$NO_2{\cdot}C_6H_4{\cdot}N_2{\cdot}SO_2Ph$	291	8·83	0·449	538	74	$4{\cdot}7_4$
$2:4:6$-$C_6H_2Br_3{\cdot}N_2{\cdot}SO_2Ph$	483	5·05	0·697	514	91	$4{\cdot}5_9$

* Evaluated as $k(_\infty P_2 - R_L)^{0.5}$, where $k = 0{\cdot}221$ at 25° and $0{\cdot}223$ at 30°.

TABLE 3. *Absorptions of diazosulphones.*

R in $R{\cdot}N_2{\cdot}SO_2Ph$	$\lambda_{max.}$ ($\log_{10}\varepsilon$)	$\lambda_{max.}$ ($\log_{10}\varepsilon$)	R in $R{\cdot}N_2{\cdot}SO_2Ph$	$\lambda_{max.}$ ($\log_{10}\varepsilon$)	$\lambda_{max.}$ ($\log_{10}\varepsilon$)
C_6H_5	295 (4·1)	425 (2·3)	p-$Br{\cdot}C_6H_4$	280 (4·1)	450 (2·6)
o-$Cl{\cdot}C_6H_4$	296 (4·0)	435 (2·35)	p-$NO_2{\cdot}C_6H_4$	260 (4·8)	410 (3·0)
p-$Cl{\cdot}C_6H_4$	295 (4·4)	415 (3·1)	$2:4:6$-$C_6H_2Br_3$	260 (3·8)	445 (2·8)

Discussion.—The spectra of the unilluminated solutions show absorptions around 300 and 420 mμ with intensities corresponding to $\log_{10}\varepsilon$ between 4 and 5 and *ca.* 3, respectively. These are features common to most diazo-compounds (Le Fèvre and Wilson, *J.*, 1949, 1106; Freeman and Le Fèvre, *J.*, 1951, 415). The curves for the *o*- and the *p*-chloro-compound are almost identical, except for the uniformly lower absorptions of the former; this difference of intensity may be due to slight steric interference between the substituent and the azo-group.

By the action of sunlight the absorption, particularly that in the 300 mμ region, was changed. Very little evidence of reversal on storage of an irradiated solution in the dark could be noted. Decomposition and formation of tar was clearly visible with the *p*-chloro- and the *p*-nitro-derivative, and similar behaviour was therefore inferred with the other substances. In these respects the situation is reminiscent more of the triazens (Le Fèvre and Liddicoet, *loc. cit.*) than of the alkali diazosulphonates (*J.*, 1951, 415).

The dielectric constants give clearer signs of reversibility. Reference to Table 1 shows that in all cases illumination alters ε_{12} (usually causing an increase). Although darkness does not completely restore the initial value, nevertheless our observations on the last three compounds are compatible with (reversible) photo-productions of new species—possibly the *cis*-isomers—accompanied by considerable (irreversible) photo-decompositions.

The reliable *a priori* estimation of the relative magnitudes of the moments of *cis*- and *trans*-diazosulphones is made difficult by the possibility of intra-molecular rotation about the N–S link. Some stabilisation of the molecule in a planar configuration may result from conjugation across the sulphone group (Koch and Moffitt, *Trans. Faraday Soc.*, 1951, **47**, 7). We note, however, that the polarity now reported for *p*-chlorobenzenediazophenylsulphone (4·3—4·4 D) is close to that of 4-chlorodiphenylsulphone (given as 4·42 D by Bergmann and Tschudnowsky, *Ber.*, 1932, **65**, 446). Evidently the vectors associated with the C–Cl and SO_2 groups interact similarly in both molecules, a fact which is most reconcilable with a *trans*-configuration of the N:N unit.

Finally, it may be mentioned that the steric considerations set out by Freeman and Le Fèvre (*loc. cit.*) for the *cis*-diazosulphonates should apply *a fortiori* to the (unknown) *cis*-diazosulphones, for which we would therefore predict a high degree of instability, a forecast in line with their non-isolation.

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650. *The Polarities and Ultra-violet Spectra of Phenyl* p-*Tolyl Azoxysulphone and its Dialkylamino-derivatives.*

By H. C. FREEMAN, R. J. W. LE FÈVRE, (MISS) J. NORTHCOTT, and C. V. WORTH.

The moment of phenyl *p*-tolyl azoxysulphone is found to be 6·0 D. This is increased to 8·5 D in the *p*-dimethylamino- and to 8·9 D in the *p*-diethylamino-derivative. These polarity changes can be explained by mesomerism. The spectra between 2300 and 4700 Å of all three substances in alcohol are recorded. With the dialkylamino-azoxysulphones two bands are found, that at longer wave-length being the more intense. The spectrum of phenyl *p*-tolyl azoxysulphone resembles that of azoxybenzene in the 300-mμ region. No indications of *cis-trans*-isomerism have been detected by the usual tests.

THE experiments described in the preceding paper suggested an exploratory examination of the azoxysulphones. These substances, unknown to Hantzsch, were discovered fairly recently by Farrar and Gulland (*J.*, 1944, 368) through the interaction of nitrosoaryls with chloramine-T or -B in pyridine solution:

$$C_6H_4R\cdot N{:}O + C_6H_4R'\cdot SO_2\cdot NNaCl \longrightarrow$$

$$C_6H_4R\cdot \underset{\underset{O}{\|}}{N}\rightarrow N\cdot SO_2\cdot C_6H_4R' \longleftrightarrow C_6H_4R\cdot \underset{\underset{O}{\downarrow}}{N}{=}N\cdot SO_2\cdot C_6H_4R'$$

When R and R′ were both hydrocarbon radicals the azoxysulphones produced were pale yellow and readily soluble in non-polar liquids; when however R was NR_2 the colours were greatly deepened and the solubilities diminished.

For the present purposes we have taken phenyl *p*-tolyl azoxysulphone (R = H, R′ = Me) as an example of the former and *p*-dimethylamino- and -diethylamino-phenyl

p-tolyl azoxysulphones (R = NMe_2 or NEt_2, R′ = Me) as examples of the latter type. In appearance, m. p., etc., each sample agreed with the description given by Farrer and Gulland. Before we determined their apparent dipole moments (in benzene) and ultra-violet absorption spectra (in alcohol), preliminary tests were made on the effects of sunlight on such solutions. These revealed no changes of dielectric constant or transmission. The precautions against illumination (cf. previous paper) usually adopted by us when handling azo-derivatives were therefore not necessary in these cases.

Polarisations.—Table 1 presents the dielectric constant, density, and concentration data necessary for the calculations of the moments shown in Table 2. Owing to their small

TABLE 1. *Densities and dielectric constants * of three azoxysulphones in benzene at 30°.*

	Phenyl p-*tolyl azoxysulphone.*				
10^6w_2	7742	16,128	24,893	33,093	44,180
ε^{30}	2·3709	2·4873	2·6150	2·7281	2·8853
d_4^{30}	0·86954	0·87199	0·87484	0·87748	0·88086
	p-*Dimethylaminophenyl* p-*tolyl azoxysulphone.*				
10^6w_2	1342	2098	2173	3690	6388
ε^{30}	2·2954	2·3145	2·3153	2·3521	2·4132
d_4^{30}	0·86754	0·86785	0·86784	0·86834	0·86907
	p-*Diethylaminophenyl* p-*tolyl azoxysulphone.*				
10^6w_2	1431	2115	2515	3139	
ε^{30}	2·2982	2·3142	2·3238	2·3391	
d_4^{30}	0·86757	0·86790	0·86797	0·86819	

* For $10^6w_2 = 0$, $\varepsilon^{30} = 2·2628$ and $d_4^{30} = 0·86718$.

TABLE 2. *Polarisations and dipole moments.*

Azoxysulphone	M_2	Mean $\alpha\varepsilon_2$	Mean β	$_\infty P_2$ (c.c.)	$[R_L]_D$ * (c.c.)	μ (D)
Phenyl *p*-tolyl	276·3	14·1	0·355	803	76	$6·0_1$
p-Dimethylaminophenyl *p*-tolyl-	319·4	24·0	0·348	1531	91	$8·4_6$
p-Diethylaminophenyl *p*-tolyl- ...	347·4	24·4	0·365	1689	100	$8·8_9$

* Estimated from observed $[R_L]_D$ for *trans*-azoxybenzene (63·6 c.c.; von Auwers, *Annalen*, 1932, **499**, 131), together with $R_{SO_2} = 7·8$ c.c. and other constants as listed by Vogel (*J.*, 1948, 1842).

solubility, the dialkylamino-azoxysulphones were conveniently dissolved in benzene at *ca.* 60° and the solutions then cooled to 30° for measurement. Recrystallisation was seldom observed, nor—to judge from the constancy of the $\alpha\varepsilon_2$ figures—did this treatment cause decomposition.

Discussion.—In the preceding paper the moment of Ph·N:N·SO_2·Ph has been recorded as 4·2 D, *i.e.*, some 1·8 D less than the corresponding value for phenyl *p*-tolyl azoxysulphone (6·0 D). Between *trans*-azoxybenzene and *trans*-azobenzene there is a similar difference (Calderbank and Le Fèvre, *J.*, 1948, 1949), which suggests that the real structures of the pale yellow azoxysulphones should be formulated with the $-N{=}N^-$ unit as in azoxybenzene,

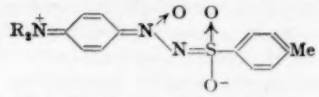
$$-N{=}N^-$$
$$\downarrow$$
$$O$$

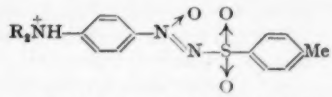
and that the contribution from the alternative, $-N{\rightarrow}N-$, offered by Farrar and Gulland,

$$-N{\rightarrow}N-$$
$$\|$$
$$O$$

is small. The increases of polarity following the introduction of *p*-NR_2 groups are parallel to those observed with the nitrosobenzenes (PhNO, 3·1 D; *p*-$Me_2N{\cdot}C_6H_4{\cdot}NO$, 6·9 D; *p*-$Et_2N{\cdot}C_6H_4{\cdot}NO$, 7·2 D; Le Fèvre and Smith, *J.*, 1932, 2239) and like them are obviously due to mesomerism, since in the absence of extended resonance a NR_2 group should not alter a molecular resultant by much more than 1·6 D, *i.e.*, the moment of a dialkylaniline (Marsden and Sutton, *J.*, 1936, 599; Barclay, Le Fèvre, and Smythe, *Trans. Faraday Soc.*, 1951, **47**, 357). Our present results thus support the opinion of Farrar and Gulland that the polar natures of the amino-azoxysulphones arise from quinonoid forms such as (I); the formation, in strong acids, of colourless salts is consistent with this since a cation of

structure (II) will be unable to mesomerise towards (I) and should therefore not have more colour than if the NR_2 group were absent.

(I) 

 (II)

Absorption Spectra.—The absorptions between 2200 and 5500 Å of alcoholic solutions of the azoxysulphones are shown in Figs. 1 and 2. They, as well as the curves shown in

FIG. 1. FIG. 2.

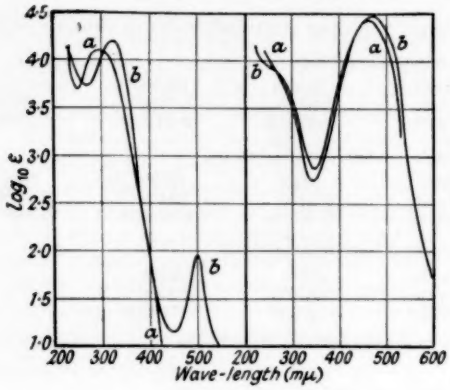


FIG. 1.

a, $C_6H_5 \cdot NO{:}N \cdot SO_2 \cdot C_6H_4Me$.
b, $C_6H_5 \cdot NO{:}N \cdot C_6H_5$.

FIG. 2.

a, $p\text{-}Me_2N \cdot C_6H_4 \cdot NO{:}N \cdot SO_2 \cdot C_6H_4Me$.
b, $p\text{-}Et_2N \cdot C_6H_4 \cdot NO{:}N \cdot SO_2 \cdot C_6H_4Me$.

FIG. 3. FIG. 4. FIG. 5.

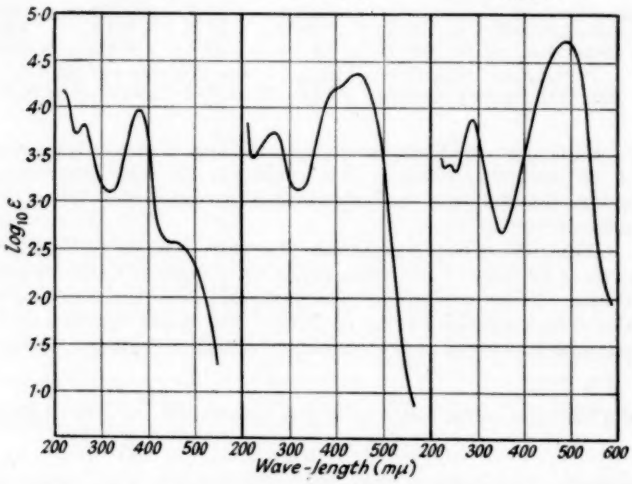


FIG. 3.

$p\text{-}Et_2N \cdot C_6H_4 \cdot N_2 \cdot SO_2 \cdot C_6H_5$.

FIG. 4.

$p\text{-}Et_2N \cdot C_6H_4 \cdot N_2 \cdot SO_3Na$.

FIG. 5.

$p\text{-}Et_2N \cdot C_6H_4 \cdot N_2 \cdot CN$.

Figs. 3—5, were determined with the Beckman Photoelectric Spectrophotometer, model D.U. Details of the maxima recorded are included in Table 3.

Two observations are notable: (*a*) the general similarity of the spectrum of phenyl *p*-tolyl azoxysulphone with that of *trans*-azoxybenzene (cf. Fig. 1), and (*b*) the particularly strong absorption shown by both of the dialkylamino-derivatives in the visible region, and the apparently reduced wave-lengths of their other absorptions.

The first point is not unexpected, since many aromatic azo- and azoxy-containing molecules possess certain common spectral features. These usually consist of: (i) a band

TABLE 3. *Alterations of* $\lambda_{max.}$ (mμ) *and* $\log_{10}\varepsilon$ (*in parentheses*) *due to* p-*dialkylamination.*

	Compound	*E*-Bands		*K*-Bands		*R*-Bands		Solvent	Refs.
A,	Ph·CH=CH·Ph	200 (4·4)	226 (4·2)	295 (4·4)	305 * (4·4)	—		EtOH	Calvin and Alter, *J. Chem. Phys.*, 1951, **19**, 765
	p-$Me_2N·C_6H_4$·CH=CH·Ph		238 (4·1)	346 (4·5)		—		EtOH	Haddow *et al.*, *Phil. Trans.*, 1948, **241**, *A*, 146
B,	Ph·N=N·Ph		—	320 (4·2)		450 (2·5)		EtOH	Le Fèvre and Wilson, *J.*, 1951, 1814
	p-$H_2N·C_6H_4$·N=N·Ph		—	362 (4·4)		—		EtOH	Burawoy, *J.*, 1937, 1865
C,	Ph·NO=N·Ph		—	320 (4·2)		—		EtOH	Present work
	p-$H_2N·C_6H_4$·NO=N·Ph		250 (4·2)	420 (4·5)		—		EtOH	Szegö, *Ber.*, 1928, **61**, 2087; 1929, **62**, 736
D,	*p*-$Cl·C_6H_4·N_2·CN$		235 (3·9)	338 (4·3)		438 (2·5)		Et_2O	Le Fèvre and Wilson, *J.*, 1950, 1106.
	p-$Et_2N·C_6H_4·N_2·CN$	241 (3·4)	285 (3·9)	492 (4·7)		—		EtOH	Present work
E,	Ph·$N_2·SO_2Na$		—	278 *		417		H_2O	Hantzsch and Lifschitz, *Ber.*, 1912, **45**, 3011
	o-$Cl·C_6H_4·N_2·SO_2Na$		228 * (3·8)	292 (3·9)		423 (2·3)		H_2O	Freeman and Le Fèvre, *J.*, 1951, 415
	p-$Et_2N·C_6H_4·N_2·SO_2Na$		266 (3·7)	395 * (4·2)	445 (4·4)	—		H_2O	Present work
F,	Ph·$N_2·SO_2$·Ph		—	295 (4·1)		425 (2·3)		EtOH	Preceding paper
	p-$Cl·C_6H_4·N_2·SO_2$·Ph		—	295 (4·4)		415 (3·1)	533 (2·3)	EtOH	Preceding paper
	p-$Et_2N·C_6H_4·N_2·SO_2$·Ph		261 (3·8)	380 (4·0)		460 (2·6)		EtOH	Present work
G,	Ph·NO=N·$SO_2·C_6H_4Me$		—	290 (4·1)		500 (2·0)		EtOH	Present work
	p-$Et_2N·C_6H_4$·NO=N·$SO_2·C_6H_4Me$		247 * (4·0)	465 (4·5)		—		EtOH	Present work

* Denotes an inflexion.

near 220—250 mμ with intensity corresponding to ε = *ca.* 10^4; (ii) a second high-intensity band with ε = *ca.* 10^4 near 300 mμ; and (iii) a band near 450 mμ with ε = *ca.* 10^2. Feature (i) appears to be characteristic of the aromatic system, thus being a benzene—" E "—band (Braude, *Ann. Reports*, 1945, **42**, 105). Such bands are typically affected by auxochromic substituents in a manner similar to ethylenic bands in aliphatic compounds, maximum displacements to longer wave-length being caused by groups with lone-pair electrons, *viz.*, $-NH_2$ and $-SH$ (compare $CH_2{:}CH{\cdot}CH{:}CH_2$, $\lambda_{max.}$ = 217 mμ, with $CH_2{:}CH{\cdot}CH{:}CHNEt_2$, $\lambda_{max.}$ = 281 mμ, in hexane).

Feature (ii), the second intense absorption, is due (Braude, *loc. cit.*) to conjugation between aromatic nuclei and substituents. That the 320-mμ band of azobenzene is of the class " K " is inferred from the following comparison: $Ph{\cdot}CH{:}CH_2$, $\lambda_{max.}$ = 244 mμ (ε = $1{\cdot}2 \times 10^4$); *trans*-Ph·CH:CH·Ph, 295 mμ ($2{\cdot}7 \times 10^4$); *trans*-Ph·N:N·Ph, 320 mμ ($1{\cdot}6 \times 10^4$). This band is not altered greatly either by substituents in the aromatic ring or in *cis*-isomers, although in the latter as well as in some *ortho*-substituted compounds non-planarity due to steric hindrance is shown by smaller intensities of absorption (cf., *e.g.*, preceding paper).

Feature (iii) for the azo-series is usually ascribed to the −N=N− linkage itself (Burawoy, *J.*, 1937, 1865; Cook, Jones, and Polya, *J.*, 1939, 1315).

The question now arises, to which class the 465-mμ bands of the *p*-dialkylaminobenzene *p'*-tolyl azoxysulphones belong. At first sight these correspond to the R-bands occurring at comparable wave-lengths with other azo-compounds, in which event the K-absorption found at 290 mμ for the parent azoxysulphone would be represented by the weaker band at 240—250 mμ. It seems doubly unlikely that this assignment is correct: first, in view of the high intensity (log ε = 4—5) of the longer-wave band in comparison with the usual intensity of R-bands ($\log_{10}$ ε *ca.* 3), and secondly, since a lowering of the absorption wave-length by a *p*-dialkylamino-substituent would be unexpected.

Alternatively, we may regard the spectral features of the two NR_2-compounds as displaced E- and K-bands. The expected intensification, due to extended resonance, for the K-bands would then be realised. While a shift after *p*-dialkylamination of 175 mμ (13,000 $cm.^{-1}$) is unusually large, there are at least some known similar cases, designated *A*—*C* in Table 3. Stilbene has been included to illustrate the analogy between the series containing −CH=CH− and −N=N−; and it is to be noted that the effect of replacing H by NR_2 in azoxybenzene (100 mμ) is much greater than that in azobenzene (43 mμ). To provide further confirmation, the absorptions of *p*-diethylaminobenzene-diazocyanide, -diazosulphonate, and -diazosulphone have been measured (Figs. 3—5). The results, with those for the azoxysulphones, are also shown in Table 3, *D*—*G*, in which the values for the NR_2-derivatives are juxtaposed with those for the parent compound and/or a halogen derivative. The three new NEt_2-compounds show, respectively, K-band shifts of 154, 165, and 85 mμ (9300, 3500, 7600 $cm.^{-1}$). From these figures, as well as from the general parallelism of the spectral characteristics of " ordinary " azo-compounds on the one hand and their *p*-NR_2-derivatives on the other, the conclusion that the 465-mμ bands of *p*-$NR_2{\cdot}Ph{\cdot}NO{:}N{\cdot}SO_2{\cdot}C_6H_4Me$ are abnormally displaced K-bands seems inescapable.

Experimental

p-Diethylaminobenzenediazocyanide, m. p. 111·5° (Found: N, 28·8. $C_{11}H_{14}N_4$ requires N, 27·7%), *sodium* p-*diethylaminobenzenediazosulphonate* (Found: N, 14·2. $C_{10}H_{14}O_3N_3SNa,H_2O$ requires N, 14·1%), and p-*diethylaminobenzenediazosulphone*, m. p. 127° (Found: N, 14·3. $C_{16}H_{19}O_2N_3S$ requires N, 14·3%), were prepared from an alcoholic diazonium solution obtained as follows (cf. Koenigs and Ruppelt, *Annalen*, 1934, **509**, 149): Freshly distilled *p*-diethylaminoaniline (1 ml.) was dissolved in a mixture of absolute ethanol (7·5 ml.) and 10N-hydrochloric acid (1 ml.). Amyl nitrite (1·5 ml.; freshly distilled) in ethanol (1·5 ml.), then added slowly at 5°, gave a green solution from which the solid diazonium salt was, however, not obtained on the addition of ether (such treatment merely yielded a yellow oil). The green solution produced the above derivatives on addition, respectively, to a concentrated solution of potassium cyanide (0·6 g.), a solution of crystalline sodium sulphite (2 g.) and sodium carbonate (3 g.) in water (25 ml.), and a solution of sodium benzenesulphinate (1 g.) in water (5 ml.) acidified with acetic acid. The diazocyanide gave deep-red leaflets by recrystallisation from alcohol, the diazosulphonate yellow plates from water (in which it was extremely soluble),

and the diazosulphone bright red needles from alcohol. The analysis reported above for the diethylaminodiazocyanide, although unsatisfactory, was obtained again after further crystallisation. From the preparative route followed, and from the recorded experience of Hantzsch, it is possible that our specimen contained a small amount of the HCN addition product, $C_{12}H_{15}N_5$ (Calc.: N, 30·6%).

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651. *The Hemicelluloses present in Aspen Wood* (Populus tremuloides). *Part II.**

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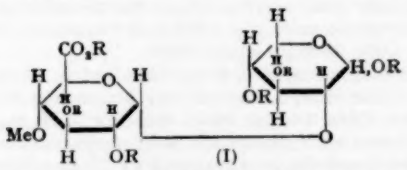
Fractionation of the uronic acids produced on hydrolysis of aspen sawdust has yielded D-galacturonic acid and 2-α-(4-methyl D-glucuronosyl) α-D-xylose as well as several unidentified acidic fractions of higher molecular weight.

IN Part I,* the isolation from the hydrolysis products of aspen wood of 4-methyl D-glucuronic acid and its identification were described. In addition, evidence was given for the presence of other uronic acid-containing materials. Two of these have been identified as D-galacturonic acid and as 2-α-(4-methyl D-glucuronosyl) D-xylose (I; R = H). The presence of D-galacturonic acid was proved by its oxidation to mucic acid and its conversion into the methyl ester of α-methyl-D-galacturonoside and into 2 : 3 : 4 : 6-tetramethyl *N*-phenyl-D-galactosylamine. The identification of this acid confirms the work of Anderson and Wise (*Paper Ind. Paper World*, 1945, **27**, No. 7, 1037).

The identification of the aldobiuronic acid depends on the following evidence. On hydrolysis, which required very drastic conditions and caused extensive degradation, D-xylose and 4-methyl D-glucuronic acid were produced. Methylation of the aldobiuronic acid with sodium hydroxide and methyl sulphate, followed by methylation with Purdie's reagents, yielded the fully methylated derivative (I; R = Me). This material was very resistant to hydrolysis by aqueous acids, but on long boiling was cleaved with extensive decomposition, yielding 2 : 3 : 4-trimethyl D-glucuronic acid, identified as the amide of the corresponding α-methylglycoside. 3 : 4-Dimethyl D-xylose was also produced and was characterised by its rate of movement on the chromatogram and by its conversion into a crystalline aniline derivative and a lactone which had properties closely similar to those of 3 : 4-dimethyl D-xylonolactone (James and Smith, *J.*, 1945, 744). The methylated aldobiuronic acid was hydrolysed with less decomposition if subjected first to methanolysis and then to hydrolysis by aqueous acids.



(I)

When (I; R = Me) was reduced with lithium aluminium hydride, a glucosyl xylose derivative was produced which, on methylation with Purdie's reagents, yielded 3 : 4-dimethyl 2-(2 : 3 : 4 : 6-tetramethyl D-glucosyl) methylxyloside. The sugar residues were probably joined by an α-linkage as this material possessed a high positive rotation. On hydrolysis with dilute aqueous acids, better yields of the xylose derivative were produced (compare above). The methylated xylose and methylated glucose were separated by chromatography on filter paper, and characterised as the crystalline aniline derivative and lactone and as the crystalline sugar and aniline derivative respectively. The lactone, on reaction with ammonia, gave a syrupy amide which gave a positive Weerman reaction (cf. James and Smith, *loc. cit.*). The dimethyl sugar (which is differentiated from

* Part I, *J.*, 1952, 2750.

2 : 3- and 2 : 4-dimethylxylose on the chromatogram), on methylation with Purdie's reagents, followed by hydrolysis with dilute acid, yielded 2 : 3 : 4-trimethyl D-xylose. These facts prove that the derivative of xylose is the 3 : 4-dimethyl compound.

A fraction containing both the aldobiuronic acid and D-galacturonic acid was oxidised with bromine water and the product methylated with sodium hydroxide and methyl sulphate. Isolation of the methylated acidic material and further methylation led to the crystalline dimethyl ester of 2 : 3 : 4 : 5-tetramethyl galactosaccharate. This provides further proof of the presence of galacturonic acid in the mixture of acids produced on hydrolysis of aspen wood. No derivative of xylonic acid could be isolated.

Galacturonic acid and the (4-methyl glucuronosyl) xylose move at the rate of galactose and glucose on the paper chromatogram when solvent C (see Experimental section) is employed. Examination of the mixture of uronic acids produced on hydrolysis of aspen sawdust showed that several other uronic acid derivatives which moved at slower rates were also present. On hydrolysis, they gave a mixture of sugars provisionally identified as galactose, xylose, rhamnose, and glucuronic and 4-methyl glucuronic acids. The origin of these acids and of (I; R = H) and of the galacturonic acid is uncertain, but it is possible that the former is produced by hydrolysis of xylan and the latter from pectic acid (cf. Anderson and Wise, *loc. cit.*).

Experimental

The following solvents (vol./vol.) were used to separate the sugars and their derivatives: (A) butanol–ethanol–water (40 : 11 : 19), (B) butanol–pyridine–water (10 : 3 : 3), (C) ethyl acetate–acetic acid–formic acid–water (18 : 3 : 1 : 4), and (D) ethanol–benzene–water (47 : 169 : 15; top layer). The R_G values quoted are given to show the positions of the sugars on the chromatogram relative to 2 : 3 : 4 : 6-tetramethyl glucose; they are not absolute values.

Optical rotations were observed at 20°.

The acids were prepared by hydrolysis of aspen wood with hot N-sulphuric acid and were separated, first on columns of charcoal and then by elution from columns of cellulose (see Part I, which describes Fraction BII).

Identification of 2-(4-*Methyl* D-*Glucuronosyl*) D-*Xylose*.—Fraction BII (0·54 g.) was boiled under reflux with methanolic hydrogen chloride (4% w/v; 50 c.c.) for 24 hours. The solution was then evaporated to 10 c.c., N-hydrochloric acid (40 c.c.) added, and the solution boiled for a further 20 hours. The cooled solution was neutralised with silver carbonate and filtered, and the silver ions were removed from the filtrate by hydrogen sulphide. The filtered solution was concentrated to 5 c.c., and a portion examined on the chromatogram with solvent C on the Whatman No. 1 paper. Xylose, 4-methyl glucuronic acid, and unchanged aldobiuronic acid were detected. The remaining solution was evaporated to a syrup which was separated into its components by chromatography on two large sheets of filter paper (solvent C). Extraction of the appropriate strips of paper gave D-xylose, m. p. and mixed m. p. 144°, $[\alpha]_D$ +18° (equil. in water) and 4-methyl D-glucuronic acid, $[\alpha]_D$ +80° (*c*, 0·6 in water) (Found: OMe, 13·3; equiv., 210. Calc. for $C_7H_{12}O_7$: OMe, 14·9%; equiv., 208).

Methylation.—The aldobiuronic acid (0·9 g.), dissolved in water, was exactly neutralised with barium hydroxide. The filtered solution was evaporated to dryness and the residual barium salt (1·04 g.) (Found: OMe, 5·4; Ba, 16·0. Calc. for $C_{24}H_{38}O_{22}Ba$: OMe, 7·6; Ba, 16·8%. 15·4 mg. gave, on distillation with phosphoric acid, furfuraldehyde equivalent to 6 mg. of xylose) was methylated by dissolving it in water (5 c.c.) and adding methyl sulphate (2 c.c.) and then sodium hydroxide (30%; 5 c.c.) dropwise with vigorous stirring and cooling. When the solution no longer reduced Fehling's solution (24 hours), an excess of 30% sodium hydroxide (10 c.c.) was added and methyl sulphate (5 c.c.) added dropwise with stirring during 24 hours. The solution was then heated on the boiling-water bath for 30 minutes, cooled, acidified with 2N-sulphuric acid, and extracted continuously with chloroform. Concentration of the extract yielded a syrup (1·0 g.) which was further methylated with silver oxide and methyl iodide and distilled [yield, 0·72 g.; b. p. 190° (bath-temp.)/0·01 mm.; n_D^{19} 1·4638; $[\alpha]_D^{20}$ +101° (in water, *c*, 0·3)] (Found: OMe, 48·5. Calc. for $C_{18}H_{32}O_{11}$: OMe, 51·3%). This methylated ester glycoside was very difficult to hydrolyse: after 24 hours in boiling 2N-sulphuric acid, less than half had been hydrolysed and the products had suffered extensive decomposition with formation of furfuraldehyde. Accordingly, it (0·32 g.) was boiled with methanolic hydrogen chloride (5% w/v; 25 c.c.) for 48 hours, the solution then evaporated to 5 c.c., N-hydrochloric acid

(20 c.c.) added, and the solution boiled for a further day. The cooled solution was neutralised with barium hydroxide, concentrated to 10 c.c., and exhaustively extracted with chloroform, thus giving 3 : 4-dimethyl D-xylose (111 mg.). The aqueous solution was then acidified with sulphuric acid and exhaustively extracted with chloroform to give 2 : 3 : 4-trimethyl D-glucuronic acid (130 mg.).

Identification of 3 : 4-*Dimethyl* D-*Xylose.*—(a) This sugar showed $[\alpha]_D^{20}$ +31°±5° (*c*, 0·57 in methyl alcohol). In solvent (A), it had R_G 0·74 and gave a reddish spot, whereas the 2 : 4- and the 2 : 3-isomer had R_G 0·73 and 0·85 respectively and gave spots of a purplish colour with the *p*-anisidine hydrochloride spray. In solvent (B), the R_G values were 0·85 for the 3 : 4-isomer and 0·84 for the 2 : 4-isomer, in solvent (C) 0·78 and 0·75, and in solvent (D) 0·47 and 0·31 respectively.

(b) *Oxidation with metaperiodate.* The sugar (29 mg.) was dissolved in water (4 c.c.) and oxidised with 0·25M-sodium metaperiodate solution (1 c.c.). Initially, the sugar could be detected on the paper chromatogram, but after 24 hours it was no longer detectable and a new sugar derivative appeared, which moved faster and gave a different colour (brown instead of red) with the *p*-anisidine hydrochloride spray. Ethylene glycol was added to the reaction mixture and the liberated acid titrated with 0·02N-sodium hydroxide (Found : 3·5 c.c. Calc. : 8·1 c.c.). Further quantities of acid (1·1 c.c.; 0·02N) were later slowly produced (from the hydrolysis of a formyl ester ?).

(c) *Oxidation with bromine water.* The sugar (61 mg.) was oxidised with bromine water (5 c.c.) for 48 hours, whereafter it could no longer be detected as such on the paper chromatogram (solvent B). Bromine was removed by aëration and the solution neutralised with silver carbonate and filtered. Silver ions were removed from the filtrate by passage of hydrogen sulphide, whereupon the solution was again filtered. Concentration of this filtrate yielded 3 : 4-dimethyl D-xylonolactone (51 mg.) which crystallised spontaneously. It was purified by distillation and had b. p. 120° (bath-temp.)/0·1 mm., m. p. 67° (from ether)((Found : OMe, 34·0. Calc. for $C_7H_{12}O_5$: OMe, 35·2%). The lactone mutarotates at the rate of a pyranolactone in aqueous solution : $[\alpha]_D^{20}$ (*c*, 2·0 in water), −51° (30 minutes); −46° (7 hours); −35° (23½ hours); −23° (49 hours; constant). James and Smith (*loc. cit.*) record m. p. 68°, $[\alpha]_D^{18}$ −54° ⟶ −27° (65 hours) for this compound.

A portion of the lactone (8 mg.) with methanolic ammonia gave a syrupy amide (8 mg.). On oxidation with sodium hypochlorite under the conditions described by James and Smith (*loc. cit.*), this gave sodium cyanate, detected as hydrazodicarbonamide (2 mg.), m. p. 258° (decomp).

Identification of the Uronic Acid Fraction.—(a) The uronic acid fraction (111 mg.) was found on the chromatogram (solvent C) to consist of 2 : 3 : 4-trimethyl D-glucuronic acid (mainly) and 3 : 4-dimethyl 2-α-(2 : 3 : 4-trimethyl D-glucuronosyl) D-xylose (?) (see below). On boiling with methanolic hydrogen chloride (25 c.c.; 1% w/v), esterification and glycoside formation took place simultaneously, with the production mainly of the methyl ester of 2 : 3 : 4-trimethyl α-methyl-D-glucuronoside. This was isolated as a syrup after neutralisation of the cooled methanolic solution with silver carbonate and concentration of the filtrate. When the crude ester glycoside was dissolved in methanol and the solution saturated with ammonia, the corresponding amide (10 mg.) was produced, having m. p. and mixed m. p. 188° (from acetone–light petroleum), $[\alpha]_D$ +150° (*c*, 0·1 in water). The residual crude amide was boiled with methanolic hydrogen chloride (25 c.c.; 3% w/v), and the crude ester isolated as described above. This was reduced to the glucose derivative by addition of the ester in ether to a solution of lithium aluminium hydride (0·5 g.) in ether. Excess of the reagent was destroyed after 15 minutes, by addition of ethyl acetate. The solution was filtered and the filtrate and washings were deionised with Amberlite IR-400 and IR-120, and evaporated to a syrup (80 mg.). Examination on the chromatogram of the products of hydrolysis (solvent A) of a portion of this fraction showed the presence of a dimethyl pentose and of a trimethyl hexose derivative. The syrup was methylated (Purdie's reagents) and hydrolysed with N-hydrochloric acid. The sugars (50 mg.), isolated in the usual way, were found on the chromatogram (solvent D) to consist of 3 : 4-dimethyl D-xylose, 2 : 3 : 4-trimethyl D-xylose and 2 : 3 : 4 : 6-tetramethyl D-glucose, the last greatly predominating. The sugars were separated on a sheet of filter paper (Whatman No. 1) (solvent A). After extraction of the appropriate section of the chromatogram, tetramethyl D-glucose (28 mg.) was obtained, having m. p. and mixed m. p. 90° with previous sintering at 86°. The aniline derivative prepared from this material in the usual manner had m. p. 114° on recrystallisation from light petroleum (b. p. 40—60°), raised to 138° on recrystallisation from alcohol, and $[\alpha]_D^{20}$ was +200° (*c*, 0·5 in acetone). A specimen of tetramethyl *N*-phenylglucosylamine was, therefore, prepared from authentic material and found to possess m. p. 114° on

recrystallisation from light petroleum (b. p. 40—60°), not depressed on admixture with the above sample, but raised to 138° on recrystallisation from alcohol.

(b) *Oxidiation with metaperiodate at 2°.* The barium salt (122 mg.) was dissolved in water (5 c.c.), and sodium sulphate (100 mg.) added, followed by 0·1M-sodium metaperiodate (20 c.c.). At intervals, portions of the solution (2 c.c.) were withdrawn, ethylene glycol added, and the liberated formic acid titrated [Found: c.c. of 0·01N-formic acid per 122 mg. of barium salt, 6·3 (½ hour), 11·2 (1½ hours), 18 (3·1 hours), 26·2 (6 hours), 34·2 (7½ hours), 86·2 (23 hours), 102·4 (70 hours); iodine was liberated after 100 hours].

(c) *Oxidation with bromine water.* The barium salt (1·05 g.) was dissolved in water (10 c.c.), and barium benzoate (1·6 g.) and bromine (2 c.c.) were added. After 48 hours, the solution failed to reduce Fehling's solution. Bromine was removed by aëration, benzoic acid was filtered off, and the solution concentrated to dryness. The residue (2·7 g.) was methylated with sodium hydroxide and methyl sulphate in the usual manner. Addition of the sodium hydroxide solution caused the reaction mixture to develop a dark orange colour. After addition of methyl sulphate (10 c.c.) and sodium hydroxide (20 c.c.; 30%), the solution was heated on the boiling-water bath for 30 minutes, cooled, acidified with 2N-sulphuric acid, and extracted exhaustively with chloroform. Concentration of the extracts gave a syrup (0·29 g.) which contained crystals. This was difficult to purify; accordingly, it was methylated with Purdie's reagents and the product (0·29 g.) distilled. The product, the dimethyl ester of 2 : 3 : 4 : 5-tetramethyl galactosaccharate (0·15 g.), b. p. 120° (bath-temp.)/0·1 mm., crystallised. Recrystallised from light petroleum (b. p. 60—80°), it had m. p. 104° (Found: OMe, 61·1; equiv., 146. Calc. for $C_{12}H_{22}O_8$: OMe, 63·3%; equiv., 147).

Methylation of Fraction BID (cf. Part I).—This acidic fraction {1·3 g.; $[\alpha]_D^{20}$ +51° (*c*, 13·0 in water)} was titrated with barium hydroxide and the neutral solution evaporated to dryness. The barium salt (1·38 g.) (Found: Ba, 16·0; OMe, 5·4%) was observed on the chromatogram (solvent C) to contain two components, one moving at the rate of glucose and the other at the rate of galactose. The sugars did not move in solvent B. The mixture of barium salts (1·3 g.) was dissolved in water (10 c.c.) and methylated by the addition of methyl sulphate (10 c.c.) and sodium hydroxide (30%) dropwise, with vigorous stirring. After 12 hours, an excess of 30% sodium hydroxide (20 c.c.) was added and the methylation continued by portion-wise addition of the methyl sulphate. After 48 hours, the solution was heated on the boiling-water bath for 30 minutes, cooled, acidified with 2N-sulphuric acid, and extracted exhaustively with chloroform. Concentration of the extracts gave a syrup (1·12 g.) which was further methylated with Purdie's reagents. The resulting neutral syrup was reduced with lithium aluminium hydride (2 g.) in ether during 30 minutes. Excess of the reagent was destroyed with ethyl acetate, and water was then added to the solution. The slurry was filtered and the precipitate well washed with water. The combined alkaline filtrates were concentrated to *ca.* 10 c.c. and exhaustively extracted with chloroform. The syrup (0·91 g.) resulting from concentration of the chloroform solution was further methylated with silver oxide and methyl iodide, and the resulting syrup (0·90 g.) distilled, giving: fraction I (0·21 g.), mainly tetramethyl methyl D-galactoside, b. p. 120° (bath-temp.)/0·1 mm., n_D^{18} 1·4495 (Found: OMe, 60·8. Calc. for $C_{11}H_{22}O_6$: OMe, 62%); fraction II (0·57 g.), methylated glucosidyl xylose, b. p. 200° (bath-temp.)/0·1 mm. (Found: OMe, 51·6. Calc. for $C_{18}H_{34}O_{10}$: OMe, 52·9%).

Fraction I (0·2 g.) was hydrolysed with boiling N-sulphuric acid (10 c.c.) {$[\alpha]_D^{20}$ +50° ⟶ +70° (constant) in 5 hours}. The solution was neutralised with barium hydroxide and exhaustively extracted with chloroform. Concentration of the extract gave a syrupy mixture of sugars (0·188 g.), n_D^{20} 1·4600, $[\alpha]_D^{20}$ +75° (*c*, 1·88 in water). Examination on the paper chromatogram (solvent A) indicated the presence of tetramethyl galactose and traces of tetramethyl glucose and trimethyl xylose. Accordingly, the syrup was boiled with alcoholic aniline for 2 hours. Concentration then gave 2 : 3 : 4 : 6-tetramethyl *N*-phenyl-D-galactosylamine, m. p. and mixed m. p. 191°, $[\alpha]_D^{20}$ −80° ⟶ +40° (*c*, 0·3 in acetone), which moved at the same rate on the chromatogram as did an authentic sample (solvent B). A small quantity of the aniline derivative dissolved in N-hydrochloric acid gave 2 : 3 : 4 : 6-tetramethyl galactose which moved at the same rate in solvent (B) as did the sugar from an authentic sample of aniline derivative which had been treated similarly. No other crystalline aniline derivative was isolated.

Fraction II (0·55 g.) was hydrolysed with boiling N-sulphuric acid (10 c.c.) for 13 hours {$[\alpha]_D^{20}$ +104° ⟶ +47° (constant) (*c*, 5·5 in N-sulphuric acid)}. The cooled solution was neutralised with barium hydroxide and exhaustively extracted with chloroform, yielding a syrup (0·60 g.). This gave spots on the chromatogram (solvent C) corresponding to 2 : 3 : 4 : 6-tetramethyl glucose, 3 : 4-dimethyl xylose, and traces of trimethyl hexose and monomethyl

pentose. The sugars were separated on paper sheet chromatograms, solvent (A) being used to irrigate the papers. Concentration of the appropriate sections of paper gave 2 : 3 : 4 : 6-tetramethyl D-glucose (0·32 g.), m. p. and mixed m. p. 93°, $[\alpha]_D^{20}$ +83° (*c*, 0·26 in water) (aniline derivative, m. p. and mixed m. p. 138°), and syrupy 3 : 4-dimethyl D-xylose (0·16 g.), characterised as its crystalline lactone, m. p. and mixed m. p. 67°, and as its aniline *derivative* (prepared in the usual manner), m. p. 121° (R_G 1·08 in solvent B) (Found: C, 61·5; H, 7·8; N, 5·5. $C_{13}H_{19}O_4N$ requires C, 61·7; H, 7·6; N, 5·5; OMe, 24·5%). The aniline derivative is unstable and darkens rapidly in air.

Methylation of 3 : 4-*Dimethyl Xylose.*—The sugar (25 mg.) was methylated with Purdie's reagents, and the product (20 mg.) isolated in the usual way. The syrup, n_D^{20} 1·4440, was hydrolysed with N-sulphuric acid (5 c.c.) on the boiling-water bath for 5 hours and the sugar isolated by continuous extraction of the neutralised solution (sodium hydroxide) with chloroform. The sugar (16 mg.) had m. p. 91°, not depressed on admixture with an authentic specimen of 2 : 3 : 4-trimethyl D-xylose.

Fraction BIE.—Identification of D-*galacturonic acid.* This fraction, $[\alpha]_D^{20}$ +63° (*c*, 7·0 in water), was neutralised with barium hydroxide, and the isolated barium salt examined (Found: Ba, 21·2; OMe, 1·5%. Calc. for the barium salt of galacturonic acid: Ba, 26·7%). A sample of the barium salt (100 mg.) was warmed with bromine water for 3 hours. White crystals separated. They were filtered off and washed with water, alcohol, and ether [yield, 21 mg.; m. p. 221° (decomp.), not depressed on admixture with mucic acid (cf. Anderson and Wise, *loc. cit.*)]. A further sample of the barium salt (0·7 g.) was dissolved in water, and barium ions were removed with Amberlite resin IR-120. The acidic solution was concentrated to a syrup which was boiled with methanolic hydrogen chloride (1%; 50 c.c.) for 12 hours. The cooled solution was neutralised with silver carbonate and filtered, and the filtrate concentrated to a syrup (0·7 g.) which crystallised. The crystals were filtered off and recrystallised from moist acetone, yielding the hydrate of the methyl ester of α-methyl-D-galacturonoside, m. p. and mixed m. p. 143° (0·2 g.), $[\alpha]_D^{20}$ +124° (*c*, 0·2 in water). This material moved at the same rate as did rhamnose on the paper chromatogram in solvent (B). The syrupy residue contained at least five components, four of which moved faster than did the above derivative of galacturonic acid on the chromatogram in solvent (B).

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652. *An Investigation of the Polysaccharide Components of Certain Fresh-water Algæ.*

By L. HOUGH, J. K. N. JONES, and W. H. WADMAN.

Polysaccharides have been isolated from the fresh-water algæ, *Nitella*, *Oscillatoria*, and *Nostoc*. The polysaccharide content of *Nitella* was composed largely of a cellulose-like polyglucosan. *Oscillatoria* contained an amylopectin-like polyglucosan, whereas *Nostoc* yielded a mucilaginous complex acidic polysaccharide containing at least six different monosaccharide units.

THE carbohydrates occurring in marine algæ have been the subject of much investigation because of their widespread occurrence and commercial importance. Little is known, however, concerning the algæ which play a dominant rôle in the vegetation of fresh water. For this reason and because it has been suggested that some fresh-water algæ might be used as a food we decided to investigate the three readily available fresh-water algæ, *Nitella*, *Nostoc*, and *Oscillatoria*.

The *Nitella* (class, Chlorophyceæ; order, Charales; family, Characeæ) was cleaned, washed with alcohol to remove fats and chlorophyll, dried, and milled to a fine brown powder. Preliminary experiments showed that no more than a trace of carbohydrate was extracted by methanol, hot water, cold dilute alkali, or hot dilute alkali.

The dry, powdered *Nitella* was freed from a large quantity of non-carbohydrate material by treatment with hot concentrated alkali, and the residual polysaccharide was isolated (25% yield). The neutral product gave no colour with iodine and was soluble in cuprammonium hydroxide solution; examination of the acid-hydrolysis products of the neutral material on the paper chromatogram showed the presence of glucose. The material was then exhaustively methylated with methyl sulphate and sodium hydroxide in an atmosphere of nitrogen. After de-ionisation by shaking the chloroform solution with a mixture of Amberlite resins IR.120 and IR.400, the methylated material had properties similar to those shown by a normal methylated cellulose, the optical rotation ($[\alpha]_D$ −15°) indicating the β-1 : 4-type of linkage. An examination of the fission products on the paper chromatogram showed the presence of 2 : 3 : 6-trimethyl glucose with a small quantity of dimethyl glucose; no tetramethyl glucose was discernible. Parallel experiments showed that the procedure will detect less than one part of tetramethyl in a hundred parts of trimethyl glucose, and therefore the methylated material probably contains little or no end-group and has a chain length greater than one hundred glucose units.

Separation of the fission products of the methylated polysaccharide by partition chromatography yielded 2 : 3 : 6-trimethyl D-glucose in 93% yield, and a mixture of dimethyl glucoses in 4% yield. The dimethyl sugars probably arise from incomplete methylation and from demethylation during the hydrolysis procedure (cf. Hirst, Hough, and Jones, *J.*, 1949, 928; Barker, Bourne, and Wilkinson, *J.*, 1950, 3027).

Thus, the high yield of 2 : 3 : 6-trimethyl D-glucose, the large chain-length, and the optical rotation of the methylated material, considered together with the properties of the original polysaccharide, show that the main carbohydrate component of *Nitella*, when harvested in November, is a cellulose. Percival and Ross (*J.*, 1949, 3041) have observed that marine-algal cellulose is essentially the same as cotton cellulose.

Both *Nostoc* and *Oscillatoria* are blue-green algæ (class, Cyanophyceæ; order, Nostocales). The free *Oscillatoria* was steeped in alcohol and dried under reduced pressure to a pale green powder. This crude material yielded little polysaccharide on extraction with either hot water or cold dilute alkali, but extraction with hot dilute alkali yielded a mixture of protein and polysaccharide. Examination of the hydrolysis products of this mixture on the paper chromatogram indicated that the main carbohydrate component was glucose, but that it also contained a little rhamnose and xylose. It was thought improbable that the rhamnose and xylose were an integral part of the polyglucosan. This was proved to be the case by the isolation by fractionation of a polyglucosan, free from xylose and rhamnose, from the crude material. The polysaccharide was similar to amylopectin and glycogen in that it was readily soluble in cold water, had a high positive optical rotation, gave a reddish-brown colour with iodine, and on hydrolysis yielded D-glucose only.

Further evidence was afforded by an examination of the product obtained by methylation. The methylated material shows a high positive optical rotation, and an examination of the fission products on the paper chromatogram showed the presence of trimethyl glucose and smaller quantities of tetramethyl and dimethyl glucoses. A quantitative estimate of the proportions of these sugars by the method of Hirst, Hough, and Jones (*loc. cit.*) indicated an average chain length of 26 glucose units per non-reducing end group. A further estimate by the method of Brown and Jones (*J.*, 1947, 1344) gave an average chain length of 23 glucose units. 2 : 3 : 4 : 6-Tetramethyl D-glucose and crystalline 2 : 3 : 6-trimethyl D-glucose were isolated from the hydrolysis products by counter-current extraction; the tetramethyl derivative was converted into the characteristic crystalline anilide. Thus, it is clear that the main food-reserve carbohydrate of *Oscillatoria* is a polyglucosan of the amylopectin type.

In distinction to *Oscillatoria* and *Nitella*, *Nostoc* afforded, on extraction with hot water, a mucilaginous complex polysaccharide composed of at least five neutral sugars and, in addition, uronic acids. The purification of the mucilage was difficult and tedious, and the hydrolysis products so complex as to render analysis difficult. The purified mucilage had an equivalent weight of 595 and, on hydrolysis, approximately 60% of the component monosaccharides were rapidly liberated, there remaining a fragment much more resistant to hydrolysis. Examination of the hydrolysis products by paper chromatography suggested

the presence of rhamnose, xylose, an unknown sugar, glucose, and galactose. An examination of the graded hydrolysis products of the mucilage afforded crystalline specimens of D-galactose and D-xylose, along with the degraded mucilage which, on further hydrolysis, afforded crystalline specimens of D-galactose and rhamnose. The analytical results indicate that the xylose residues are readily removed, in contrast to the rhamnose residues which are firmly attached. The uronic acids liberated on prolonged hydrolysis were separated from the neutral sugars by use of ion-exchange resins and when examined on the paper chromatogram gave two spots only, the first corresponding in position to glucuronic acid or galacturonic acid and the second to glucurone, this indicating the presence of glucuronic acid (Partridge, *Biochem. J.*, 1947, **42**, 238). In addition, the uronic acid fraction gave a positive test for galacturonic acid with Ehrlich's reagent (*Ber.*, 1932, **65**, 352), a test not given by glucuronic or mannuronic acids (Stacey, *J.*, 1939, 1529).

The complexity of the mucilage and its stability to acid hydrolysis resulted in such severe analytical difficulties that it is not yet possible to make a precise statement concerning the relative proportion of the component monosaccharides. Nevertheless, as a rough estimate, a consideration of the equivalent weight of the mucilage indicates that it is compounded of some 30% of hexuronic acids, and the paper chromatographic analyses suggest that there is approximately 10% of rhamnose, 25% of D-xylose, and a remainder (35%) composed largely of galactose with smaller amounts of glucose and an unknown sugar.

Experimental

Nitella.—*Treatment of the raw* Nitella. The *Nitella* was harvested in November, 1947, from Lake Windermere; it was a tangled mass of long green filaments, each filament being about 2 mm. in diameter. The crude alga was thoroughly washed in large volumes of cold water to remove small impurities, large foreign bodies being then removed by hand. After being drained free from excess of moisture, it was steeped for 24 hours in each of three successive portions of alcohol (5 l.), then dried under reduced pressure at 40°, and finally milled to a fine brown powder.

Trial extractions. A small portion of the dry powdered *Nitella* was extracted with successive portions of methanol, hot water for 6 hours, 0·5N-sodium hydroxide for 24 hours at 18°, and for 3 hours at 100° with a further portion of the same reagent. Each aqueous extract was poured into an excess of alcohol and only in the case of the hot alkali extract was an appreciable precipitate formed which proved, on hydrolysis, to be largely proteinaceous.

Preparation of the crude cellulose. The remainder of the material (184 g.) was treated with sodium hydroxide solution (25%) for 3 hours at 100°, and the insoluble crude cellulose filtered off, thoroughly washed with water and then alcohol, and dried under reduced pressure (yield 47 g.). The product was largely soluble in cuprammonium hydroxide solution.

Hydrolysis of the crude cellulose. A portion (*ca.* 0·1 g.) was heated with N-sulphuric acid (25 c.c.) at 100° for 12 hours in a sealed tube. The acid, in which was suspended a small amount of flocculent material, was neutralised with barium carbonate, filtered, and the filtrate reduced to a syrup. Examination of this syrup on the paper chromatogram showed it to contain glucose.

Methylation of the crude cellulose. The crude cellulose (20 g.) was repeatedly methylated with methyl sulphate and sodium hydroxide in an atmosphere of nitrogen. After six methylations the product was extracted with chloroform, and the extract filtered, dried (Na_2SO_4), de-ionised with a mixture of Amberlite resin, IR.120 and IR.400, and evaporated to a syrup under reduced pressure (yield, 17·1 g.) (Found: OMe, 44·4; sulphated ash, 0·6%). This had $[\alpha]_D$ −14·9° (*c*, 2·3 in chloroform).

Hydrolysis of the methylated cellulose. A portion (330 mg.) was heated with acetic acid–methanol (1 : 1 v/v) containing hydrogen chloride (3%) in a sealed tube at 100° for 12 hours. The contents were then evaporated under reduced pressure at room temperature to a small volume and heated for a further 12 hours with aqueous hydrochloric acid (3%). The solution was neutralised with silver carbonate, filtered, de-ionised with a mixture of Amberlite IR.120 and IR.400, and evaporated to a syrup (330 mg., 92% yield).

2 : 3 : 6-*Trimethyl* D-*glucose.* A portion of the hydrolysis products (130 mg.) was separated on a sheet-paper chromatogram, butanol–ethanol–water (4 : 1·1 : 1·9 v/v) being used as the mobile phase. After the resultant chromatogram had been dried, the appropriate parts of the paper were extracted with hot methanol in a micro-Soxhlet apparatus and yielded dimethyl

glucoses (*ca.* 5 mg.) and 2 : 3 ; 6-trimethyl D-glucose (121 mg.; m. p. 114°) which after two crystallisations from ether had m. p. and mixed m. p. 121°; $[\alpha]_D^{19}$ +71° (equilibrium value; *c*, 6·9 in water) (Found : OMe, 41·1. Calc. for $C_9H_{18}O_6$: OMe, 41·9%).

Oscillatoria.—*The raw material.* The crude wet alga was obtained from the Freshwater Biological Association, Ambleside, and was immediately steeped in an excess of alcohol for 24 hours, filtered off, steeped with acetone for 24 hours, again filtered off, and dried under reduced pressure at 40°.

Preliminary examination. A portion of the dried material was stained with a dilute iodine solution; there was a red-brown coloration, which microscopic examination showed to be due to preferential staining of certain granules within the cell.

Small portions of the dry material were extracted with cold water, hot water, cold 0·5N-alkali, and hot 0·2N-alkali, and the extracts examined for carbohydrate content. In the cold water, hot water, and cold alkali extracts appreciable quantities of carbohydrate could not be detected, but hot alkali extracted a considerable amount of material which was precipitated by a large volume of ethanol, removed by centrifugation, and hydrolysed with N-sulphuric acid, whereupon examination of the fission products on the paper chromatogram indicated that it contained glucose with a little xylose and rhamnose.

The isolation of a polyglucosan. The crude material (68 g.) was suspended in 0·2N-sodium hydroxide solution (4 l.) at 18°, and the mixture stirred for 1 hour and filtered. The residue, after being washed free from alkali, was stirred with glacial acetic acid, the mixture filtered, and the residue heated at 100° with 2N-sodium hydroxide solution (1 l.) for 1 hour and then filtered, and the precipitate thoroughly washed with hot water. The combined filtrate and washings were neutralised with glacial acetic acid, copper acetate solution (10%; 100 c.c.) was added, a small precipitate filtered off, and the filtrate, after concentration under reduced pressure to a small volume (*ca.* 200 c.c.), was poured into alcohol (3 l.). The resultant precipitate was filtered off, thoroughly washed with alcohol, and dissolved in water (400 c.c.), and the solution shaken with a mixture of Amberlite resins IR.120 and IR.400. After removal of the resins, the polysaccharide was precipitated by the addition of excess of alcohol, filtered off, washed with alcohol, and dried at 40° under reduced pressure. The neutral, white powder, $[\alpha]_D$ +188° (*c*, 2·1 in water) (Found : N, 0·6; sulphated ash, 3·2%), was readily soluble in cold water and with iodine in potassium iodide solution gave a red-brown colour.

Hydrolysis. A portion (0·37 g.) of the purified polysaccharide was dissolved in 0·5N-sulphuric acid (25 c.c.) and heated for 5 hours at 100°. After neutralisation with barium carbonate and removal of the insoluble barium salts, the solution was evaporated to dryness, extracted with hot methanol containing water (5%), and the methanol removal under reduced pressure, yielding a clear syrup (0·384 g., 93% yield), $[\alpha]_D$ +56° (*c*, 1·7 in water), which showed only glucose on examination on the paper chromatogram. The syrup crystallised to give α-D-glucose hydrate, m. p. 92—93°, $[\alpha]_D$ +110° (*c*, 0·7 in water; initial value) ⟶ +52° (equil. value).

Methylation. A portion of the polyglucosan (9·7 g.) was repeatedly methylated with methyl sulphate and sodium hydroxide, the product extracted with chloroform, the extract dried (Na_2SO_4), and the solvent evaporated under reduced pressure to yield the methylated polyglucosan (yield, 9·3 g.) (Found : OMe, 42·7; sulphated ash, 3·7%), $[\alpha]_D$ +195° (*c*, 3·6 in chloroform).

Fission of the methylated material. A portion (0·115 g.) was heated for 7 hours at 100° with methanolic hydrogen chloride (2%; 25 c.c.) in a sealed tube, after which the contents were concentrated under reduced pressure at room temperature to a small volume, and this dissolved in N-hydrochloric acid (25 c.c.) and heated at 100° for a further 5 hours. The solution was then neutralised by the addition of silver carbonate, filtered, de-ionised with a small amount of mixed Amberlite IR.4B and IR.100 resins, and evaporated under reduced pressure to a syrup (0·116 g.).

Examination of a portion on the paper chromatogram, butanol–ethanol–water (5 : 1 : 4 v/v; top layer) being used as the mobile phase and *p*-anisidine hydrochloride as the spray reagent, indicated the presence of 2 : 3 : 6-trimethyl glucose and smaller quantities of monomethyl, dimethyl, and tetramethyl glucose. In a quantitative experiment, the proportions of these methyl sugars were estimated by the alkaline hypoiodite micro-procedure (Hirst, Hough, and Jones, *loc. cit.*), a phosphate buffer being used (Chanda *et al.*, *J.*, 1950, 1289); these sugars gave, respectively, the following titres with 0·01N-thiosulphate : 6·3, 0·2, 0·9, 0·3 c.c., corresponding to an average chain-length of 26 glucose residues. Another portion (*ca.* 100 mg.) was separated on sheet-paper chromatograms, with benzene–ethanol–water (169 : 47 : 15, v/v; top layer) as the mobile phase, and, after separation, the 2 : 3 : 6-trimethyl glucose was located

by the development of test strips, and the appropriate section of the remainder of the chromatogram extracted with hot methanol in a micro-Soxhlet apparatus. Evaporation of the methanol yielded crystals (73 mg.; m. p. 109°) which, on recrystallisation twice from ether, gave crystalline 2 : 3 : 6-trimethyl D-glucose, m. p. and mixed m. p. 121°, $[\alpha]_D^{19}$ +71° (equilibrium value, *c*, 1·0 in water) (Found : OMe, 42·7. Calc. for $C_9H_{18}O_6$: OMe, 41·9%), which on the paper chromatogram gave only one discrete spot indistinguishable in R_G value and colour reactions from a genuine specimen. In another experiment, the methylated polyglucosan (0·97 g.) was dissolved in 2% methanolic hydrogen chloride (50 c.c.) and heated under reflux for 7 hours. The solution was neutralised with silver carbonate, filtered, and evaporated under reduced pressure at room temperature, and the methyl glycosides (0·971 g.) were dissolved in water (50 c.c.). The fully methylated sugar was isolated from the mixture by Brown and Jones's quantitative procedure (*J.*, 1947, 1344), whereby the aqueous solution is continuously extracted with light petroleum (b. p. 38—40°), two glass continuous extractors being used, one above the other. The first extract obtained after 4½ hours, a mixture (0·101 g.) of " tri " and " tetra," was dissolved in water (50 c.c.) and extracted once again with light petroleum to give tetramethyl methylglucopyranoside (44·2 mg.), the yield corresponding to an average chain-length of 23 glucose residues. The tetramethyl methyglucoside was hydrolysed in N-sulphuric acid for 5 hours, after which the acid was removed on an ion-exchange column to give syrupy 2 : 3 : 4 : 6-tetramethyl D-glucose [26 mg.; $[\alpha]_D$ +83° (*c*, 1·3 in water)] which, when examined on the paper chromatogram, was observed to contain traces of trimethyl glucose. The syrup gave an anilide which crystallised from light petroleum as white needles, m. p. 132° undepressed on admixture of the sample with an authentic specimen of 2 : 3 : 4 : 6-tetramethyl D-glucose anilide.

Nostoc.—*The isolation of the mucilage.* The alga was collected in January, 1948, at the Freshwater Biological Association, Ambleside, and obtained as gelatinous nodules containing much impurity. Several nodules were selected and observed to contain on the average 97% of water. The bulk of the material (8·5 kg.) was thoroughly washed with water, steeped in two successive portions of methylated spirits for 24 hours in each, and then in ether for 24 hours. The material was then dried under reduced pressure. Since it contained much extraneous matter, the hard nodules of *Nostoc* were isolated by hand picking. This material (44 g.) was boiled with water (4 l.) for 3 hours, and the resultant mucilaginous mass filtered through a muslin cloth, the residue being boiled with more water (2 l.) for ½ hour and again filtered. The combined extracts were exceedingly viscous, setting to a gel below 50°; the gel was cooled to 20°, made 0·1N with respect to hydrochloric acid, thus reducing the viscosity, and all debris removed by centrifugation. Diatomaceous earth was added to the turbid brown supernatant liquors and the solution filtered on a Buchner funnel. The clear yellow filtrate was neutralised by the addition of ammonia solution, the viscosity increasing so greatly that the solution became a gel. A solution of cupric chloride (25%; 400 c.c.) was added with stirring to this gel and subsequently ammonia solution was added until the solution just became dark blue. The insoluble copper complex and copper hydroxide were removed by filtration under reduced pressure. The filtrate gave negative tests for carbohydrate. The precipitate was washed with ethanol, followed by ethanolic hydrogen chloride (5%) until the washings were copper-free, and finally with ethanol until the washings were chloride-free. The cream-coloured product was dried ($CaCl_2$) under reduced pressure [yield, 7·3 g.; $[\alpha]_D$ +10·6° (*c*, 0·57 in water) [Found : sulphated ash, 4·1; N, 0·2%; equiv. (by alkaline titration), 780, corrected for ash, 580]. The product gave no colour with iodine, but gave a positive naphtharesorcinol test for hexuronic acid.

Purification of the mucilage. Efforts to precipitate the mucilage from aqueous solution by the addition of alcohol or acetone were fruitless, merely resulting in an increased viscosity. The following procedure was found to be of greatest utility. To a solution of a portion (200 mg.) of the mucilage in water (20 c.c.), ethanolic hydrogen chloride (1%; 30 c.c.) was added, followed by ether (30 c.c.), resulting in the formation of a bulky gelatinous precipitate which was removed, with difficulty, by centrifugation. This precipitation was repeated a further five times as above, and then a further six times, the hydrochloric acid then being omitted from the ethanol. On drying the final precipitate, a colourless solid was obtained {yield, 43 mg.; $[\alpha]_D$ +11·8 (*c*, 1·0 in water)} [Found : sulphated ash, 0·03%; equiv. (by alkaline titration), 595; N, 0·2%].

Hydrolysis of the mucilage. The mucilage (237 mg.) was dissolved in 0·5N-sulphuric acid (25 c.c.). Portions (1 c.c.) were sealed into glass tubes which were then immersed in a boiling-water bath. At intervals, the reducing power of the tube-contents was estimated by oxidation with alkaline hypoiodite (Hirst, Hough, and Jones, *loc. cit.*). Conversion of the reducing power, in terms of hexose, into a percentage of the original mucilage gave the following data :

4% (initial value), 24% (16 min.), 35% (38 min.), 43·5% (70 min.), 50% (110 min.), 56% (170 min.), 60% (275 min.), 63% (400 min.), 68% (835 min.), 70% (1270 min.), 88% (2310 min.). It is clear that the rate of hydrolysis decreases sharply after some 400 minutes and, at this stage, the contents of another tube were neutralised with 0·01N-bartya, the barium sulphate removed by centrifugation, and the supernatant liquor allowed to percolate down a column of Amberlite resin IR.100, the effluent being free from barium ions. The solution was concentrated under reduced pressure to *ca.* 0·5 c.c., and a portion transferred to the paper chromatogram, separated, and analysed as described by Hirst, Hough, and Jones (*loc. cit.*). A qualitative examination indicated the presence of rhamnose (R_G 0·31 in butanol saturated with water), xylose (R_G 0·17), an unknown sugar (R_G 0·11), glucose (R_G 0·09), galactose (R_G 0·07), and oligosaccharides. The separation of the galactose, glucose, and the unknown sugar was insufficient to allow of their separate estimation and consequently they were estimated jointly as anhydro-hexose. The quantitative experiment indicates that on partial hydrolysis the mucilage yields 6% of rhamnose, 15% of xylose, and 34% of hexose, calculated as anhydro-sugars.

Partial hydrolysis of the mucilage. A solution of the mucilage (1·35 g.) in 0·5N-sulphuric acid (100 c.c.) was heated on the boiling-water bath for 3 hours. A small precipitate (35 mg.) (protein ?) was removed, the filtrate exactly neutralised with baryta, barium sulphate removed, and the solution concentrated under reduced pressure to a yellow solid (1·37 g.). This was extracted with boiling methanol until the extracts were substantially non-reducing, leaving a residue of the barium salts of the degraded mucilage (*A*; 0·54 g.). The methanol extracts were concentrated under reduced pressure to a syrup (*B*; 0·76 g.).

Examination of syrup B. The reducing power of the syrup {$[\alpha]_D$ +26° (*c*, 2·8 in water)}, as determined by oxidation with alkaline hypoiodite, corresponded to 52% of hexose. Quantitative analysis of the sugars, by using the method described above, gave 22% of "hexose" (galactose, glucose, and the unknown sugar), and 23% of xylose; the chromatogram indicated that the sugars contained no rhamnose, but a considerable amount of oligosaccharides and uronic acid. The mixture of sugars (0·74 g.) was fractionated on a column of cellulose by using *n*-butanol half-saturated with water as the mobile phase. Fraction I (200 mg.) yielded crystalline D-xylose, which was converted into the characteristic dibenzylidene dimethylacetal {m. p. 211—212°, mixed m. p. 211°; $[\alpha]_D$ −7° (*c*, 0·8 in chloroform)}. Fraction II (120 mg.) contained, as indicated by a paper-chromatographic examination, an unknown sugar and glucose, but crystalline derivatives were not obtained. Fraction III (390 mg.) was obtained by eluting the column with water and, when examined on the paper chromatogram, showed the presence of galactose, glucose, and uronic acids. A hot methanolic extract, on concentration to a small volume and being seeded with D-galactose, yielded crystalline D-galactose, m. p. 163°, $[\alpha]_D$ +82° (equilibrium value; *c*, 0·7 in water). The total yield from the column was 710 mg. (96%).

Examination of the barium salts A. The solid, $[\alpha]_D$ +59° (*c*, 2·9 in water), contained 1 mole of reducing group per 990 g., as determined by hypoiodite oxidation. Examination on the chromatogram showed traces of xylose as the only contaminant. The barium salt (535 mg.) was heated with N-sulphuric acid (20 c.c.) at 100° for 16 hours, then filtered, and the filtrate treated with Amberlite IR.100 until it was free from barium salts. The residue (330 mg.), $[\alpha]_D$ +38° (*c*, 2·3 in water), obtained by evaporation of the filtrate to dryness [Found: equiv. (by alkaline titration), 410; reducing group, 1 mole/280 g.] was dissolved in water, the solution allowed to percolate down a column of Amberlite resin IR.4B, the column washed thoroughly with water, and the combined effluents concentrated to a syrup (95 mg.). This was shown by paper chromatogram to contain chiefly galactose and rhamnose with traces of glucose and xylose. On trituration with ethanol, D-galactose crystallised and was isolated on a porous tile. The crystals, m. p. 159°, $[\alpha]_D$ +79° equilibrium value (*c*, 1·1 in water), were converted into D-galactose methylphenylhydrazone (m. p. 179° and mixed m. p. 179—180°). The tile was extracted with hot methanol and the extract concentrated to a small volume and seeded with L-rhamnose hydrate; this gave crystals, m. p. 95° undepressed on admixture with a geniune specimen of L-rhamnose hydrate, indistinguishable from rhamnose on the paper chromatogram. The yield was too low to allow measurement of the optical rotation.

The uronic acids were isolated from the ion-exchange resin by displacement with dilute hydrochloric acid, followed by removal of the chloride ion by the addition of silver carbonate and filtration. Hydrogen sulphide was passed into the filtrate, the insoluble silver sulphide removed, and the acid filtrate concentrated under reduced pressure to a syrup (70 mg.). This was examined on the paper chromatogram alongside galacturonic and glucuronic acids, *n*-butanol–water–acetic acid (6 : 4 : 1 v/v; upper phase) being used as the mobile phase; there were two

strong spots, corresponding to galacturonic and/or glucuronic acid (both showed the same R_F value) and to glucurone, which is always associated with glucuronic acid (Partridge, *loc. cit.*). The syrup gave a brick-red precipitate when warmed with basic lead acetate, thus indicating the presence of galacturonic acid (Ehrlich, *loc. cit.*; Stacey, *loc. cit.*).

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653. *Inorganic Chromatography on Cellulose. Part XIII.* Determination of Tantalum and Niobium in Low-grade Phosphatic and Siliceous Ores.*

By R. A. Mercer and A. F. Williams.

The chromatographic method of determination of tantalum and niobium (*J.*, 1952, 3155) has been extended to ores containing less than 0·1% of the oxides of these metals. Chemical pre-treatment is required. The method has been applied to Nigerian granites containing up to 0·3% of niobium pentoxide and to phosphatic soils from Sukulu, Uganda. Phosphate ions are partially extracted with niobium in the chromatographic procedure and are removed thereafter.

Chromatographic methods have been described for the quantitative separation and determination of tantalum and niobium in medium- and high-grade minerals and ores (Part XII, *loc. cit.*). The sample, prepared in a dilute solution of hydrofluoric acid to which ammonium fluoride was added, was placed on a column of cellulose. Tantalum was extracted with ethyl methyl ketone saturated with water; the column was equilibrated with ethyl methyl ketone containing 1% of hydrofluoric acid which arrested movements of titanium, zirconium, and tin; and niobium was then extracted with ethyl methyl ketone containing 12·5% (v/v) of hydrofluoric acid (40% w/w aqueous solution). In one procedure the sample was chromatographed directly, and in the other a preliminary chemical treatment, involving "acid hydrolysis," was given in order to remove the bulk of the common metal ions from the earth acids (oxides of tantalum and niobium). For low-grade materials samples of 10 g. were needed, to yield weighable quantities of the earth acids. As these could not be directly transferred to columns of cellulose preliminary separation of the earth acids, together with small amounts of other constituents, was necessary.

Two types of ore have been examined in detail and it is considered that the principles involved could be extended to any type of low-grade material. One ore examined was a granite from Nigeria, containing small amounts of pyrochlore and about 70% of silica, together with iron, aluminium, alkali metals, and small amounts of titanium, tin, and zirconium. Silica was removed first, by repeated evaporation with hydrofluoric–nitric acids; fluoride ions were then removed by addition of sulphuric acid and evaporation to fuming; after dilution, two "acid hydrolyses" were made, thereby precipitating the earth acids together with some titanium, zirconium, and other impurities (cf. *loc. cit.*). The ignited crude earth acids were dissolved in hydrofluoric acid, and tantalum and niobium determined chromatographically.

The second ore, from Sukulu, Uganda, contained much phosphate (as apatite) and ferric oxide, minor constituents being about 0·2% of niobium (about 0·004% of tantalum) (as pyrochlore), titanium, and zirconium. It was not found practicable to separate phosphate ions completely before chromatography and, since phosphate is partly extracted with the niobium by the solvent mixture used, the niobium could not be determined by direct ignition (*loc. cit.*). Separation of the earth acids from phosphate ions was achieved by prior precipitation with ammonia solution (cupferron and tannin were unsatisfactory for this purpose). The difficulty did not affect determination of tantalum since phosphate ions are not extracted by ethyl methyl ketone saturated with water.

* Part XII, *J.*, 1952, 3155.

The chromatographic procedure has also been applied to the determination of niobium in phosphatic pyrochlore concentrates derived from Sukulu soils. However, a second precipitation of the extracted earth acid with ammonia was needed for complete separation from phosphate ions. The amount of niobium present in such samples is considerably greater than the amount obtained from the analysis of the original ore.

Experimental

Determination of Tantalum and Niobium in Low-grade Phosphatic Ores: Analysis of Soil from Sukulu, Uganda.—(a) *Separation of niobium from phosphate ions by ammonia solution.* A known amount of metallic niobium was weighed into a platinum dish, and a measured amount of ammonium phosphate solution added. Hydrofluoric acid was added together with a few drops of nitric acid, and solution effected by heating on the steam-bath. After evaporation to dryness sulphuric acid (50% v/v; 10 ml.) was added and the whole evaporated until sulphur trioxide was freely evolved (to remove fluoride). The solution was transferred to a 400-ml. beaker, diluted to 200 ml., and then neutralised with ammonia solution, and an excess of 5 ml. (*d* 0·880) was added. The solution was heated to the b. p. and set on the edge of a hot-plate for about 20 minutes. The precipitate was filtered on a No. 541 Whatman filter-paper after addition of a little cellulose pulp, washed with dilute ammonia–ammonium nitrate solution, ignited, and weighed (as Nb_2O_5). The amount of phosphate present in the filtrate was determined by the standard molybdate method. In order to test the degree of separation of niobium from phosphate ions, a second precipitation of the niobium oxide with ammonia solution was made after the ignited oxide from the first precipitation had been dissolved in hydrofluoric–nitric acid and the procedure described above was then repeated. During this work it was noticed that on ignition of niobium residues to the pentoxide in the presence of comparable amounts of phosphate ions, the resulting material was extremely resistant to attack by hydrofluoric acid, possibly owing to the formation of niobium pyrophosphate. Results obtained are shown in Table 1 (values are mg.). The figures for phosphate are not quantitative (some phosphoric acid is lost during the evaporation with sulphuric acid) but serve as a guide to the degree of separation.

Table 1.

Nb present	P_2O_5 present	Nb_2O_5 found (1st pptn.)	P_2O_5 in filtrate (1st pptn.)	Nb_2O_5 found (2nd pptn.)	P_2O_5 in filtrate (2nd pptn.)	Nb_2O_5 found (3rd pptn.)	P_2O_5 in filtrate (3rd pptn.)
99·6	*ca.* 90	109·5	74	98	11·0	—	—
102·6	,, 50	107	41·6	100·7	6·0	—	—
100·2	,, 25	102·1	18·9	98·7	4·0	98·3	nil
31·6	,, 60	31·7	60·2	29·8	2·8	29·0	nil
32·8	,, 50	37·0	41·0	32·5	3·2	—	—
37·5	,, 25	41·3	20·2	37·0	2·2	—	—

The results show that two precipitations with ammonia suffice for the separation of the earth acid from phosphate ions but that there is a small loss of niobium. Nevertheless, it is considered that the process is sufficiently accurate for most analytical purposes. Preliminary investigations of cupferron and tannin as reagents for the precipitation of niobium showed only poor separation from phosphate ions.

(b) *Behaviour of phosphate ions in the chromatographic procedure.* The movement of phosphate ions during the chromatographic extraction of tantalum and niobium was examined for two types of sample, namely, (1) calcium phosphate, and (2) calcium phosphate together with tantalum and niobium.

The samples were decomposed with hydrofluoric–nitric acid in the usual way, and the chromatographic procedure described earlier (*loc. cit.*) was then carried out. The tantalum and niobium were determined in the appropriate fractions and all fractions were analysed for phosphate content. The niobium was reprecipitated twice with ammonia to test the completeness of the separation from phosphate ions. Results obtained are given in Table 2. They show that phosphate ions are only extracted by the solvent employed for extraction of niobium. Two precipitations with ammonia are required for the separation of niobium from 100 mg. of P_2O_5 such as might be present after extraction of a phosphatic niobium concentrate (see also Tables 1 and 5). In the analysis of low-grade Sukulu soil, where relatively small amounts of Nb_2O_5 (and correspondingly small amounts of P_2O_5) are present, one precipitation of niobium was sufficient (see Table 3).

The results show that phosphoric acid is not extracted by the solvent employed for extraction of tantalum, so the direct ignition procedure may be employed for the final determination of tantalum as Ta_2O_5.

TABLE 2. *Sample* (1): 137 *mg. of* P_2O_5 (*as calcium phosphate*).
Sample (2): 140 *mg. of* P_2O_5 (*as calcium phosphate*), 57·2 *mg. of* Ta, *and* 101·5 *mg. of* Nb.

Sample	Ta fraction: 250 ml. of COMeEt satd. with H_2O		Intermediate fraction: 400 ml. of COMeEt containing 1% of HF		Nb fraction: 400 ml. of COMeEt containing 12·5% of HF					
					1st pptn.		2nd pptn.		3rd pptn.	
	Ta found (mg.)	P_2O_5 extracted (mg.)	"Nb" found (mg.)	P_2O_5 extracted (mg.)	"Nb" (mg.)	P_2O_5 in filtrate (mg.)	"Nb" (mg.)	P_2O_5 in filtrate (mg.)	"Nb" (mg.)	P_2O_5 in filtrate, (mg.)
1	Nil	Nil	Nil	trace	Nil	31	—	—	—	—
2	57·8 *	Nil	Nil	Nil	113·4	81	101·4	14·8	100·0	1·4

* Ta determined by pptn. with ammonia.

TABLE 3.

Sample no.	Nb_2O_5 (mg.) added as concentrate	1st precipitation		2nd precipitation	
		Nb_2O_5 (mg.)	P_2O_5 in filtrate (mg.)	Nb_2O_5 (mg.)	P_2O_5 in filtrate (mg.)
S.1	Nil	26·8	—	24·4	—
S.1	Nil	23·7	—	22·7	—
S.1	24·5	48·2	—	46·5	—
S.2	Nil	19·0	21·0	18·0	0·3
S.3	Nil	13·4	20·0	11·4	0·2

(c) *Procedure for analysis of phosphatic Sukulu soil.* The method adopted was as follows: A sample (10 g.) was treated with hydrochloric acid (18%; 100 ml.), vigorously boiled, and evaporated, finally to dryness; a further small quantity of hydrochloric acid was then added, and the solution again evaporated to dryness. The residue was baked under an infra-red lamp for 1 hour to effect removal of small quantities of fluoride (possibly originating in cryolite). As is shown below (p. 3402) for analysis of Nigerian granite, hydrochloric acid treatment followed by baking does not remove gross amounts of fluoride such as remain after hydrofluoric acid treatment for removal of silica. If fluoride is present during "acid hydrolysis," low results are obtained.

To the dry residue obtained, concentrated hydrochloric acid (5 ml.) was added, followed by water (250 ml.) and saturated sulphur dioxide solution (30 ml.), and the solution boiled for 20 minutes and then set aside overnight (see Bagshawe and Elwell, *J. Soc. Chem. Ind.*, 1947, **66**, 398). The precipitate, containing the earth acids, was filtered on No. 541 Whatman filter-paper and, after being washed with warm 0·5N-hydrochloric acid, treated with 18% hydrochloric acid (100 ml.) and hydrogen peroxide (100-vol.; 30 ml.). The filter-paper was ashed in a platinum dish, and the ash added to the above mixture, which was then warmed for a few minutes, diluted to about 600 ml., and boiled gently for about 30 minutes: during this process the volume of the solution was not allowed to fall below *ca.* 500 ml. After being kept for *ca.* 1 hour the precipitate was filtered off (paper pulp was added) on No. 541 Whatman filter-paper, washed with 0·5% hydrochloric acid and reserved for further treatment. The filtrate was neutralised with ammonia, and concentrated hydrochloric acid (10 ml.) then added, followed by saturated sulphur dioxide solution (*ca.* 30 ml.). The volume of solution at this stage was 500—600 ml. The solution was boiled for 30 minutes and then set aside overnight. After filtration, the precipitate, combined with the first precipitate, was ignited in a platinum dish. The ignited precipitate contained, in addition to earth acids (mainly niobium), silica, phosphates of calcium and common metal ions, and small amounts of titanium and zirconium. The ignited precipitate was dissolved in hydrofluoric acid and treated as a sample for chromatographic analysis (*loc. cit.*). The fraction of solvent used for extraction of tantalum and the intermediate solvent fraction were discarded, as the tantalum content of Sukulu soil was of the order of the blank, and the intermediate solvent fraction was free from metal ions. After removal of solvent the niobium fraction was transferred to a platinum dish, sulphuric acid (50% v/v; 10 ml.) was added, and the whole evaporated to fuming. After about 30 minutes' fuming, niobium was determined as above after precipitation with ammonia. Table 3 shows some results for the determination of niobium in Sukulu soil (the tantalum content was too low for determination). In one case pyrochlore concentrate (derived from the soil) was added. A single precipitation of

earth acid with ammonia is seen to suffice for separation of niobium from phosphate ions. A small loss of niobium occurred during the second precipitation with ammonia.

Table 4 shows results for a range of Sukulu soil samples. In a number of analyses known amounts of niobium were added in the form of pyrochlore concentrate and good recoveries were obtained. In two further experiments, analysed ferrotantalum–niobium alloy was added, and in another a known amount of columbite. The results showed good recoveries of tantalum.

TABLE 4.

Sample no. (10 g.)	Nb–Ta added as:	Ta_2O_5 added (mg.)	Nb_2O_5 added (mg.)	Ta_2O_5 found (mg.)	Nb_2O_5 found (mg.)	Nb_2O_5 present (%)	Nb_2O_5 found (%)
4	Nil	Nil	Nil	*ca.* 1·0	19	0·19	0·19
4	Ferro–Ta–Nb	5·7	26	7·6	46	0·45	0·46
4	Pyrochlore	—	23·5	*ca.* 1·0	44	0·43	0·44
7	Nil	Nil	Nil	*ca.* 1·0	23	0·23	0·23
7	Columbite	15·6	19	15·1	35	0·42	0·35
7	Pyrochlore	—	24·5	*ca.* 1·0	48	0·48	0·48
7	,,	—	49	,,	72	0·68	0·72
7	,,	—	76	,,	105	0·99	1·05
7	,,	—	20·0	1·7	45·1	0·43	0·45
7	,,	—	38·0	3·1	60·0	0·61	0·60

TABLE 5.

Ta_2O_5 found (mg.)	1st pptn. "Nb_2O_5" (mg.)	1st pptn. P_2O_5 in filtrate (mg.)	2nd pptn. Nb_2O_5 (mg.)	2nd pptn. P_2O_5 in filtrate (mg.)	3rd pptn. Nb_2O_5 (mg.)	3rd pptn. P_2O_5 in filtrate (mg.)	Ta_2O_5 (%)	Nb_2O_5 (%)
3·2 *	103·7 †	59·0	96·4	7·6	94·6	Nil	0·2	9·6

* Blank = 1 mg.
† 4·5 Mg. included from last 200 ml. of " intermediate solvent " fraction.

Typical results of spectrographic analysis of separated Nb_2O_5: Ta, 0·1; Fe, 0·1; Sn, 0·01; Ti, 0·3; Zr, 0·3—1·0%; P, trace. The total impurities in the Nb_2O_5 are thus negligible.

(d) *Analysis of phosphatic pyrochlore concentrate from Sukulu soil.* The concentrate obtained from the soil was analysed by the chemical-chromatographic procedure (*loc. cit.*). Niobium was determined in the appropriate solvent fraction (from a 1-g. sample) by ammonia precipitation. The results, in Table 5, show that two precipitations with ammonia are necessary (see also Tables 1 and 2) for separation of earth acid from phosphate ions.

Determination of Tantalum and Niobium in Low-grade Siliceous Ores from which Phosphates are Absent: Application to Nigerian Granite.—Nigerian granite containing small amounts of pyrochlore comprises about 70% of silica together with iron, aluminium, potassium, and sodium, with small amounts of other common metals, titanium, and zirconium. The content of niobium pentoxide ranged from 0·2 to 0·3%, tantalum being approx. 1/12th of this. From a sample (*ca.* 10 g.) in a platinum dish (diam. 5", to avoid spraying) silica was removed by repeated evaporation with hydrofluoric acid after the addition of a few ml. of concentrated nitric acid. Sulphuric acid solution (50% v/v; 40 ml.) was added and the mixture evaporated under an infra-red lamp until sulphur trioxide was freely evolved, and finally to dryness by bringing the dish close to the lamp. A further 40 ml. of sulphuric acid were added and the mixture was again evaporated to fuming and allowed to fume for a further 20—30 minutes. [In early experiments attempts were made to remove fluoride ions by evaporations with hydrochloric acid (the sample being finally taken to dryness and baked) but very low results were obtained in the subsequent determination of niobium. This indicated that fluoride ions were present during the acid hydrolysis and caused solubility of the earth acids.] The contents of the dish were transferred to a 1-l. beaker with the aid of water. Insoluble material adhering to the dish was removed by digestion with a little hydrochloric acid. The crude earth acids were then precipitated by two acid hydrolyses as described on p. 3401. Apart from a few ml. of hydrochloric acid employed to clean the dish, no more was added for the first precipitation since sufficient acid was present as sulphuric acid. After ignition of the crude earth acid precipitate, tantalum and niobium were determined chromatographically. It was found that the intermediate solvent fraction (ethyl methyl ketone containing 1% of hydrofluoric acid) could be discarded. Results obtained on a sample of the Nigerian granite with and without the addition of known amounts of pyro-

chlore concentrate (analysed by the direct procedure, *loc. cit.*), separated from the source of the sample, are given in Table 6. They show excellent recoveries of the earth acids.

TABLE 6. *Pyrochlore concentrate contains* 3·01% *of* Ta_2O_5 *and* 36·6% *of* Nb_2O_5. *Samples taken,* 10 *g.*

Concentrate added equiv. to :		Found		Present		Found	
Ta_2O_5 (mg.)	Nb_2O_5 (mg.)	Ta_2O_5 (mg.)	Nb_2O_5 (mg.)	Ta_2O_5 (%)	Nb_2O_5 (%)	Ta_2O_5 (%)	Nb_2O_5 (%)
Nil	Nil	3·0 *	28·0	—	—	0·02	0·28
Nil	Nil	2·5	25·1	—	—	0·02	0·25
6·1	73·5	9·6	99·5	0·08	1·00	0·09	1·00
6·6	79·0	8·8	103·0	0·09	1·05	0·08	1·03

* Blank = 1 mg.

As a precautionary measure niobium was determined in the appropriate solvent fraction by precipitation with ammonia before chromatography in case small amounts of potassium salts had been occluded by the crude earth acids, for potassium ions are extracted by the solvent employed for extraction of niobium. Spectrographic analysis of the ignited niobium pentoxide showed that the impurities present were negligible.

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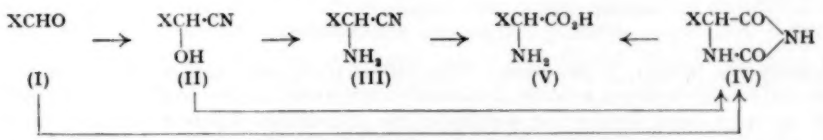
654. *Experiments in the Synthesis of Methionine.*

By D. O. HOLLAND and J. H. C. NAYLER.

The synthesis of methionine from β-methylthiopropaldehyde *via* α-amino-γ-methylthiobutyronitrile and *via* 5-2′-methylthioethylhydantoin has been examined, and the action of carbon dioxide on α-amino-γ-methylthiobutyronitrile studied.

SEVERAL satisfactory syntheses of DL-methionine from β-methylthiopropaldehyde (I) have recently been reported although the original attempts by Barger and Coyne (*Biochem. J.*, 1928, **22**, 1417) to use (I) in the Zelinsky modification of the Strecker reaction resulted in an overall yield of only 6%. Syntheses *via* the amino-nitrile (III) have been described by Catch, Cook, Graham, and Heilbron (*Nature*, 1947, **159**, 578; *J.*, 1947, 1609), Pierson, Giella, and Tishler (*J. Amer. Chem. Soc.*, 1948, **70**, 1450), and in U.S.PP. 2,485,236, 2,564,105, and B.P. 605,311; Gaudry and Nadeau (*Canadian J. Res.*, 1948, **26**, *B*, 226) and Pierson *et al.* (*loc. cit.*; cf. also B.P. 630,139) have used the Bucherer–Bergs method, *via* the hydantoin (IV).



(X = $CH_3S{\cdot}CH_2{\cdot}CH_2$, throughout.)

The first route suffers from the disadvantage that hydrolysis of the crude nitrile (III) with acids gives much tar which leads to losses on subsequent isolation of the amino-acid, and several processes have been devised to obviate these losses (U.S.P. 2,432,429, 2,432,478, 2,443,391, 2,504,425). The intermediate amino-nitrile was purified as its oxalate (Catch

et al., loc. cit.), the hydrochloride being unsatisfactory (Barger and Coyne, *loc. cit.*). On hydrolysis with hydrochloric acid, however, only a 52% yield of methionine was obtained.

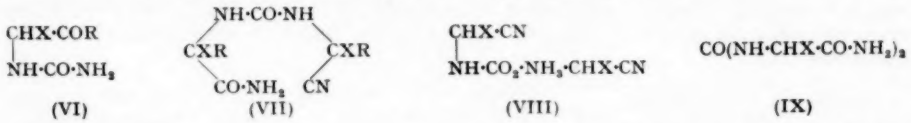
We have found the normal sulphate and the dihydrogen phosphate to be very suitable salts for the purification of the amino-nitrile, since they are formed in good yield and purity from ethyl alcohol. Subsequent acid hydrolysis did not produce tar, and methionine was readily isolated in a high state of purity and in very good yield. The precipitation of the sulphate also proved of value in assessing yields of the amino-nitrile.

Most previous workers have prepared the amino-nitrile (III) by reaction of the cyanohydrin (II) with ammonia. The only attempt to use the reaction of the aldehyde (I) with potassium cyanide and ammonium chloride in aqueous solution was by Barger and Coyne (*loc. cit.*) with very unsatisfactory results. We have found, however, that the latter method is entirely satisfactory if the reaction mixture is saturated with ammonia, the yield of amino-nitrile being about 90%. Subsequent acid hydrolysis gave methionine in 65% overall yield from the aldehyde. When ammonia was omitted the yield of amino-nitrile was only 14%.

These results parallel those of Gaudry (*Canadian J. Res.*, 1946, **24**, *B*, 301), who found that inclusion of ammonia in the Strecker reaction gave improved yields of α-amino*iso*valeronitrile from *iso*butaldehyde, and concluded that the reaction between the initial aldehyde or intermediate cyanohydrin and ammonia was an equilibrium, the presence of an excess of ammonia favouring amino-nitrile formation. It seems more probable, however, that the beneficial effect of the ammonia was to minimise the formation of the corresponding imino-dinitrile. The main product from the reaction of β-methylthiopropaldehyde with ammonium chloride and sodium cyanide, although insoluble in dilute hydrochloric acid, evidently contained only a little of the cyanohydrin (II) since it gave only a very small quantity of α-hydroxy-γ-methylthiobutyric acid on hydrolysis : it contained only a trace of unreacted aldehyde. Since the hydrochlorides of imino-dinitriles are known to be hydrolysed by water (Pinner and Lifschutz, *Ber.*, 1887, **20**, 2356) it appears likely that the bulk of the product was the dinitrile di-(1-cyano-3-methylthiopropyl)amine.

In the synthesis of methionine from β-methylthiopropaldehyde *via* 5-2′-methylthioethylhydantoin (IV) we obtained results similar to those recorded by Pierson *et al.* (*loc. cit.*), although reduction of the amount of sodium cyanide from 2·2 to 1·1 moles gave rather better yields. We could not confirm the presence of the hydantoic acid (VI; R = OH) reported by Pierson *et al.*, but isolated a small quantity of the corresponding amide (VI; R = NH_2), m. p. 173·5—174·5° (decomp.). Hill and Robson (*Biochem. J.*, 1936, **30**, 248) gave the m. p. of the acid (VI; R = OH) as 171—172°, but we find that this compound melts with decomposition at 138—139°.

Hydrolysis of 5-2′-methylthioethylhydantoin to methionine was effected in good yield by heating it under pressure with an aqueous suspension of lime. Contrary to the statement in U.S.P. 2,527,366, the product was practically as pure as that obtained when baryta was employed. Hydrolysis with lime under reflux, however, was very slow and even after 48 hours some of the acid (VI; R = OH) could be isolated.



(VI) (VII) (VIII) (IX)

Bucherer and Steiner (*J. pr. Chem.*, 1934, **140**, 291) reported that when carbon dioxide was passed into an aqueous solution of α-amino*iso*butyronitrile or α-amino-α-methylbutyronitrile at room temperature the corresponding hydantoins separated rapidly in practically quantitative yield. When this reaction was applied to α-amino-γ-methylthiobutyronitrile, a solid, m. p. 161°, separated very slowly which was formulated as *N*-(1-carbamido-3-methylthiopropyl)-*N*′-(1-cyano-3-methylthiopropyl)urea (VII; R = H). Compounds possessing this suggested structure were obtained by Bucherer and Steiner when the amino-nitriles mentioned above were allowed to react with carbon dioxide in the absence of water (VII; X = R = Me and X = Et, R = Me, respectively), and Cook, Heilbron,

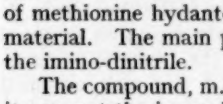
and Levy (*J.*, 1947, 1598) have described the formation of a similar compound (VII; X = Ph, R = H) from α-aminobenzyl cyanide.

After 4 days the yield of the urea (VII; R = H) was only 23% and there were also isolated small quantities of methionine hydantoin and unchanged amino-nitrile; the remainder of the product appeared to be the corresponding imino-dinitrile. When the reaction was conducted at 50° for 4 hours, none of the urea was obtained, an 18% yield of methionine hydantoin being formed instead together with 16% of unchanged starting material. The main product, insoluble in dilute hydrochloric acid, again appeared to be the imino-dinitrile.

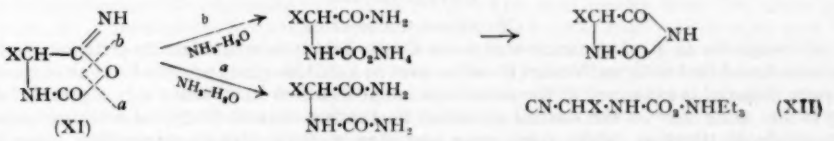
The compound, m. p. 161°, gave no effervescence on treatment with acid, showing that it was not the isomeric carbamate (VIII), and when heated with water it was converted into the corresponding amide (IX). Hydrolysis with an aqueous suspension of lime under pressure gave a 58% yield of methionine.

Bucherer and Steiner suggested that formation of both hydantoin and urea (VII) arose from amino-nitriles *via* a common labile imino-oxazolidone of type (XI) which was produced *via* a carbamic acid. It was conjectured that the intermediate rearranged to the hydantoin in the presence of water, but in its absence reacted with another molecule of the amino-nitrile to yield (VII). The postulated intermediate is closely analogous to the 5-amino-2-mercaptothiazoles described by Cook, Heilbron, and Levy (*loc. cit.*) which were found to rearrange to the corresponding dithiohydantoins on treatment with bases (Cook, Heilbron, and Stern, *J.*, 1948, 2031).

The failure of methionine nitrile to form substantial quantities of the hydantoin is probably due to its being too weak a base to effect the opening of the ring of the intermediate imino-oxazolidone (XI) to give the carbamate (X). In the same way the very slow formation of the urea (VII; R = H) is probably due to the very slight tendency of the amino-nitrile to form the initial carbamate (VIII).


(X)

The small amount of hydantoin isolated may have arisen through the presence of ammonia released by the slow breakdown of the amino-nitrile to the imino-dinitrile. The higher yield of the hydantoin from the reaction at higher temperatures supports this view, since amino-nitriles are known to yield imino-dinitriles and ammonia under these conditions. In this event it seems likely that ring fission of the hypothetical intermediate (XI) occurred at (*b*) rather than at (*a*) since the latter would be expected to yield the amide (VI; R = NH_2) under the mild conditions employed. It should be noted, however, that Slotta, Behnisch, and Szyszka (*Ber.*, 1934, **67**, 1529) have prepared hydantoins from α-amino-amides by heating them with ammonium carbonate, although the conditions used were far more drastic than those employed here.


(XI) (XII)

From the above considerations it seemed likely that if a comparatively strong base were used in the reaction of the nitrile of methionine with carbon dioxide the formation of the urea (VII; R = H) would be avoided and the reaction would be much more rapid. By including 1 mol. of triethylamine in the reaction it was, indeed, found that good yields (90%) of the hydantoin could readily be obtained, the reaction being complete in about 30 minutes.

Attempts to obtain the initial carbamate (XII) by carrying out the reaction in dry benzene gave rise to a heavy oil which failed to yield a crystalline benzyl ester on reaction with benzyl bromide. When the oil reacted with carbon disulphide in alcoholic solution, however, carbon dioxide was evolved and the corresponding crystalline dithiocarbamate was obtained, identical with the product from the direct action of the nitrile of methionine with carbon disulphide in the presence of triethylamine. Since it has already been shown

(Holland, *J.*, 1950, 2134) that carbamates can be converted into the corresponding dithiocarbamates in this way, there is reasonable confirmation that the initial reaction product is the carbamate (XII).

The dithiocarbamate was somewhat unstable, becoming brown with the release of triethylamine. A solution in hot water gave rise to a solid, m. p. 222° (decomp.), which appeared to be the expected 5-2′-methylthioethyl-2 : 4-dithiohydantoin described by Catch *et al.* (*loc. cit.*). These workers gave m. p. 212° (decomp.) but we have found that the m. p. (196°) of the initial product obtained by their method is only slowly raised on repeated recrystallisation, indicating a mixture of the dithiohydantoin and the isomeric 5-amino-2-mercapto-4-2′-methylthioethylthiazole. A similar crude product was also obtained from the mother-liquors of the product, m. p. 222° (decomp.), described above. When these crude products were refluxed with aqueous ammonia the dithiohydantoin, m. p. 222° (decomp.), was readily isolated.

An attempt to apply the reaction with carbon dioxide in the presence of triethylamine to the crude mixture obtained from β-methylthiopropaldehyde, ammonium chloride, sodium cyanide, and ammonia (excess of which was removed after amino-nitrile formation) in aqueous alcohol gave only a small amount of the urea (VII; R = H) together with triethylamine hydrochloride. This puzzling result was traced to a reaction analogous to the Solvay process for the manufacture of sodium carbonate, triethylamine taking the place of ammonia, for when carbon dioxide was passed into an aqueous-alcoholic solution of sodium chloride and triethylamine, substantial quantities of sodium hydrogen carbonate were precipitated and triethylamine hydrochloride was isolated from the mother-liquors. Triethylamine is thus removed from the reaction and the nitrile of methionine then yields only (VII; R = H). By carrying out the preparation of the nitrile of methionine in industrial spirit and filtering off the sodium chloride, conversion into the hydantoin proceeded in 85% yield.

The effect of triethylamine on the preparation of the hydantoin corresponding to methionine from the nitrile indicated that it might prove of value in the Bucherer–Bergs method, and this was, in fact, found to be so. By use of 1·1 mol. of triethylamine in the reaction and by reducing the ammonium carbonate to 2·2 mol., 90—95% yields of the hydantoin corresponding to methionine were easily obtained on keeping the reaction mixture for 18 hours at room temperature, or by boiling it for 15 minutes. Reduction of the amount of triethylamine in the reaction led to decreased yields, and attempts to replace the base partly or wholly by ammonia were also unsatisfactory. By the use of this method overall yields of pure methionine of 79% from β-methylthiopropaldehyde were obtained, the intermediate hydantoin not being isolated.

Experimental

(M. p.s are uncorrected.)

Although the m. p. of an amino-acid is not always held to be a satisfactory criterion of purity, we have found that with methionine it can be used as a reliable guide provided a control specimen of pure material is examined at the same time under identical conditions; *e.g.*, a sample behaving in the same way as the control specimen on heating showed 99·3% of methionine in the formaldehyde titration, while a less pure specimen melting with decomposition some 6—7° lower than the control had an estimated purity of 94·6%.

α-Amino-γ-methylthiobutyronitrile.—To a mixture of ammonium chloride (59 g.), sodium cyanide (53 g.), concentrated aqueous ammonia (350 ml.), and alcohol (200 ml.) saturated with ammonia, β-methylthiopropaldehyde (52 g.) was added dropwise with stirring during 30 minutes, the temperature being kept at 15—20°. After being stirred overnight, the mixture was concentrated under reduced pressure to about 300 ml. The upper oily layer that had appeared was separated, and the residual aqueous layer extracted with ether (4 × 75 ml.). After the combined oil and extracts had been dried and the solvent removed, finally under reduced pressure, the amino-nitrile remained as a mobile orange-red oil (62·1 g.; 95·5%).

Conversion of the amino-nitrile into its *sulphate* was carried out by adding dropwise the calculated quantity of sulphuric acid (8·4 ml.) to a cooled and stirred solution of the amino-nitrile (41·1 g.) in absolute alcohol (200 ml.). The salt (36·9 g.) separated at once as a cream-coloured powder, m.p. 175° (decomp.) after being washed with alcohol and ether. Addition

of a little sulphuric acid to the filtrate yielded a further 3·2 g. of sulphate, m. p. 174° (decomp.) (total yield 70·9%). Amino-nitrile regenerated from the sulphate gave a 75% yield of the salt in this way. Any considerable excess of sulphuric acid must be avoided since this causes redissolution of the sulphate. The salt was purified by dissolution in the minimum volume of cold water and addition of alcohol and separated as micro-crystals, m. p. 176° (decomp.) (Found: C, 33·2; H, 6·5; N, 15·4; S, 25·6. $C_{10}H_{20}N_4S_2,H_2SO_4$ requires C, 33·5; H, 6·2; N, 15·6; S, 26·8%).

α-Amino-γ-methylthiobutyronitrile dihydrogen phosphate separated slowly from a solution of the base in alcohol on addition of phosphoric acid as a white granular powder, m. p. 114—118°. Recrystallised from alcohol, it separated as a white powder with unchanged m. p. (Found: C, 26·2; H, 5·9; N, 12·2. $C_5H_{10}N_2S,H_3PO_4$ requires C, 26·3; H, 5·7; N, 12·3%).

S-*Benzylisothiuronium α-Hydroxy-γ-methylthiobutyrate*.—α-Hydroxy-γ-methylthiobutyronitrile [prepared from β-methylthiopropaldehyde by the method of Pierson *et al.* (*loc. cit.*)] (5 g.) was heated on the steam-bath with hydrochloric acid (5 ml.) and water (10 ml.) for 80 minutes. The resulting solution was cooled and adjusted to pH 7 with sodium hydrogen carbonate, and the small amount of oil that separated was extracted into ether. To the residual aqueous solution there was added a solution of *S*-benzyl*iso*thiuronium chloride (2 g.) in hot alcohol, and the *α-hydroxy-γ-methylthiobutyrate* (4·4 g.), m. p. 156°, separated as needles; recrystallised from water, it had m. p. 157° (Found: C, 49·2; H, 6·7; N, 9·0. $C_{13}H_{20}O_3N_2S_2$ requires C, 49·3; H, 6·4; N, 8·9%).

5-2′-*Methylthioethylhydantoin*.—(*a*) A mixture of sodium cyanide (16·2 g.), ammonium carbonate (99·0 g.), and β-methylthiopropaldehyde (30 ml.) in 50% aqueous alcohol (780 ml.) was heated for 12 hours at 50—55°. The resulting pale yellow solution was concentrated under reduced pressure to *ca.* 100 ml. and stored at 0°, yielding crude hydantoin (24·5 g.). The mother-liquors (pH 9·2) were then acidified carefully at room temperature with concentrated hydrochloric acid (27 ml.) to pH 1 to avoid ring closure of any hydantoic acid that might have been present. There was considerable effervescence as more 5-2′-methylthioethylhydantoin (22·7 g.) separated (total yield 90%). This material was quite suitable for hydrolysis to methionine. It was purified by recrystallisation from water (charcoal), separating as a white crystalline powder, m. p. 108° (lit., m. p. 103—105°) (Found: C, 41·2; H, 5·9; N, 15·7. Calc. for $C_6H_{10}O_2N_2S$: C, 41·4; H, 5·8; N, 16·1%).

(*b*) A mixture of sodium cyanide (16·2 g.), ammonium carbonate (63·6 g.), β-methylthiopropaldehyde (30 ml.), and triethylamine (45·6 ml.) in 50% aqueous alcohol (300 ml.) was kept at room temperature for 24 hours. The resulting pale yellow solution was worked up as described above to yield 89% of crude methionine hydantoin.

(*c*) Carbon dioxide was passed for 1 hour through a solution of α-amino-γ-methylthiobutyronitrile (10·9 g.) and triethylamine (11·6 ml.) in 50% aqueous alcohol (50 ml.). Next morning the mixture was concentrated under reduced pressure to about one-half of its original volume, whereupon the crude hydantoin (10·8 g.) separated. From the mother-liquors after further concentration more hydantoin (2·32 g.) separated on acidification (total yield 89·5%).

γ-Methylthio-α-ureidobutyramide (VI; R = NH_2).—The final liquors from the above preparation (*a*) of methionine hydantoin were concentrated *in vacuo* nearly to dryness and the residual yellow gum was extracted with absolute alcohol from the sodium chloride. After removal of the solvent the gum was dried *in vacuo* (NaOH) and then heated with a little ethyl acetate. When this was kept at 0° a small quantity (0·37 g.) of the *amide* separated as a white powder, which was filtered off and washed with a little ethyl acetate; it had m. p. 164—166° (decomp.). The residue from the mother-liquors when boiled with a little water gave on refrigeration a second crop (0·55 g.) of the amide, needles, m. p. 168—169° (decomp.). The combined solids, recrystallised from 80% alcohol, had m. p. 173·5—174·5° (decomp.) (Found: C, 37·8; H, 6·6; N, 22·4. $C_6H_{13}O_2N_3S$ requires C, 37·7; H, 6·8; N, 22·0%).

γ-Methylthio-α-ureidobutyric Acid (VI; R = OH).—Methionine (2 g.) and sodium cyanate (1·1 g.) were heated in water (25 ml.) on a steam-bath for 15 minutes. After cooling to room temperature the mixture was acidified with hydrochloric acid to about pH 3 and solid began to separate after a few minutes. After concentration of the reaction mixture under reduced pressure to about 10 ml. and refrigeration overnight, the precipitated hydantoic acid was filtered off and washed with a little water; it had m. p. 132—135° (decomp.). On recrystallisation from water it separated as needles, m. p. 138—139° (decomp.) (Found: C, 37·6; H, 6·8; N, 14·5. Calc. for $C_6H_{12}O_3N_2S$: C, 37·5; H, 6·3; N, 14·6%).

N-(1-*Carbamido*-3-*methylthiopropyl*)-N′-(1-*cyano*-3-*methylthiopropyl*)*urea* (VII; R = H).—Carbon dioxide was passed in a slow stream through a solution of α-amino-γ-methylthiobutyro-

nitrile (2·87 g.) in a mixture of alcohol (20 ml.) and water (15 ml.). The *urea* began to separate after 19 hours and was collected after a further 31 hours (0·41 g.; m. p. 161°). The passage of carbon dioxide through the mother-liquors was continued for a further 2 days and more product (0·36 g.), m. p. 155°, separated. The combined solids were recrystallised from alcohol, the urea separating as white microcrystals, m. p. 161° (Found: C, 43·8; H, 6·7; N, 18·0. $C_{11}H_{20}O_2N_4S_2$ requires C, 43·4; H, 6·6; N, 18·4%).

The final mother-liquors were acidified with dilute hydrochloric acid and thoroughly extracted with ether. Evaporation of the dried ether extracts left a yellow gum (1·51 g.) which partly crystallised on storage, and when rubbed with benzene gave 5-2′-methylthioethylhydantoin (0·22 g.). The residual oil gave a considerable blue precipitate when heated with aqueous sodium hydroxide and ferrous sulphate followed by the addition of ferric chloride and hydrochloric acid, but on hydrolysis with hydrochloric acid the oil failed to yield α-hydroxy-γ-methylthiobutyric acid and was therefore probably largely di-(1-cyano-3-methylthiopropyl)amine.

The acidified aqueous layer after extraction with ether was basified and re-extracted with ether, giving unchanged α-amino-γ-methylthiobutyronitrile (0·3 g.), characterised as its sulphate.

NN′-*Di*-(1-*carbamido*-3-*methylthiopropyl*)*urea*.—The urea (VII; R = H) (2·5 g.) in water (100 ml.) was heated on the steam-bath for 30 minutes, and the resulting solution concentrated *in vacuo* to leave a sticky solid. This yielded the *amide* (0·42 g.) on dissolving it in hot alcohol and cooling the solution. Recrystallisation from this solvent gave the amide as tiny needles, m. p. 216° (decomp.) (Found: C, 41·2; H, 7·4; N, 17·2. $C_{11}H_{22}O_2N_4S_2$ requires C, 41·0; H, 6·9; N, 17·4%).

Triethylammonium 1-*Cyano*-3-*methylthiopropyldithiocarbamate*.—Carbon dioxide was passed through a solution of the nitrile of methionine (1·28 g.) and triethylamine (1·4 ml.) in absolute alcohol (5 ml.) at 0° for 20 minutes. Carbon disulphide (1 ml.) was then added, and the mixture kept at room temperature. The solution rapidly became bright yellow, and a steady stream of carbon dioxide was evolved during 50 minutes. On the addition of dry ether (30 ml.) an oil separated which gradually solidified when scratched. This was filtered off and washed with ether to give the required *dithiocarbamate* (1·17 g.) as a white powder, m. p. 134° (decomp.), which rapidly turned pale yellow in air. It was purified by solution in absolute alcohol (35 ml.) and precipitation with dry ether (100 ml.); m. p. 136° (decomp.) (Found: C, 46·6; H, 8·5; N, 13·5; S, 31·8. $C_{12}H_{25}N_3S_3$ requires C, 46·9; H, 8·2; N, 13·7; S, 31·3%).

The same compound was obtained in 65% yield when carbon disulphide (2 ml.) was added to a solution of the amino-nitrile (2·44 g.) and triethylamine (2·6 ml.) in alcohol (5 ml.) at 0°, and the mixture kept for 20 minutes then diluted with ether.

5-2′-*Methylthioethyl*-2 : 4-*dithiohydantoin*.—A solution of the dithiocarbamate (1 g.) in water (10 ml.) was heated on the steam-bath; triethylamine was evolved and yellow crystals of the dithiohydantoin gradually separated. After 5 hours the solid (0·40 g.) was removed, m. p. 219° (decomp.), after shrinking and darkening from 200°. Recrystallisation from alcohol raised the m. p. to 222° (decomp.) (Found: C, 35·1; H, 4·6; N, 13·6. Calc. for $C_6H_{10}N_2S_3$: C, 34·9; H, 4·9; N, 13·6%).

Methionine.—(a) *Hydrolysis of methionine nitrile with hydrochloric acid*. The amino-nitrile (5·38 g.), regenerated from the normal sulphate, was heated under reflux with concentrated hydrochloric acid (10 ml.) for 2 hours, and the dark reaction mixture then concentrated under reduced pressure to a gum. Excess of acid was removed by two evaporations with water under reduced pressure, and the final residue was dissolved in a little water and neutralised with triethylamine. An excess of triethylamine (8 ml.) was added, and the mixture warmed and then concentrated under reduced pressure virtually to dryness. The residue was boiled with alcohol to remove the triethylamine hydrochloride, and the residual methionine washed with alcohol till free from chloride. The product (5·55 g., 90·7%) was obtained as light brown platelets, m. p. 250° (decomp.) after softening from 247° [control, m. p. 252° (decomp.)]. The amino-acid was readily purified by treating an aqueous solution with charcoal and precipitating the amino-acid with alcohol.

(b) *Hydrolysis of methionine nitrile with sulphuric and phosphoric acids*. Methionine nitrile dihydrogen phosphate (6·0 g.) was refluxed for 1·5 hours with concentrated sulphuric acid (4·5 g.) and water (4·5 ml.), and the product cooled, diluted with water (7 ml.), and neutralised with ammonia (*d* 0·88). The solid that separated was filtered off and washed with water to yield methionine (3·36 g., 85·7%), m. p. 250° (decomp.) after softening from 248° [control, m. p. 258° (decomp.)], which contained not more than a trace of sulphate. A further 0·5 g. of methionine of similar purity was obtained from the mother-liquors.

(c) *From* β-*methylthiopropaldehyde* via *methionine nitrile*. To a mixture of ammonium

chloride (29·5 g.), sodium cyanide (26·5 g.), water (350 ml.), and alcohol (200 ml.) saturated with ammonia at about 15°, β-methylthiopropaldehyde (50 ml.) was added dropwise during 30 minutes with stirring, the temperature being kept at 4—8° but then being allowed to rise to about 17° during 16 hours. The mixture was concentrated under reduced pressure, the internal temperature being kept as low as possible, till an oil began to separate. Concentrated hydrochloric acid (50 ml.) was then added, and the whole concentrated under reduced pressure to a gum. More hydrochloric acid (210 ml.) was added, and the mixture refluxed for 1·5 hours. The dark hydrolysate was freed from excess of acid in the usual way and the final black gum was dissolved in hot water (75 ml.) and treated with charcoal (15 g.), and the resulting orange solution boiled with sodium hydroxide solution (200 ml.; 40%) till ammonia ceased to be evolved. The solution was then filtered through a bed of kieselguhr to remove a little tar and adjusted to pH 6 with concentrated hydrochloric acid (76 ml.). After refrigeration, the precipitated methionine was filtered off, slurried with water (50 ml.), refiltered, washed with a little water, and dried at 100° [35·3 g.; m. p. 253—254° (decomp.)] [control, m. p. 255° (decomp.)].

The filtrate and washings were acidified with hydrochloric acid (10 ml.) and evaporated to dryness under reduced pressure. The residue was extracted twice with hot absolute alcohol (100 + 50 ml.), and the combined extracts were adjusted to pH 6 with triethylamine and refrigerated to give a second crop of methionine (12·6 g.), m. p. 250° (decomp.).

(d) *From β-methylthiopropaldehyde via methionine hydantoin.* To a mixture of sodium cyanide (16·2 g.) and ammonium carbonate (63·6 g.) in 50% aqueous alcohol (300 ml.), triethylamine (45·6 ml.) was added with stirring followed by β-methylthiopropaldehyde (30 ml.). The temperature of the mixture rose by 6—7° and remained thus for about 10 minutes and then slowly fell to room temperature. After 1 hour's stirring the mixture was kept overnight and the resulting pale yellow product was then diluted with alcohol (150 ml.); after about 15 minutes, the precipitated sodium carbonate was removed and washed with alcohol.

To the aqueous alcoholic filtrate, water (665 ml.) and barium hydroxide (200 g.) were added, and the mixture was boiled to remove the alcohol and triethylamine, then heated under reflux for 36 hours. The hydrolysate was filtered, the solid residue extracted with boiling water (300 ml.) and then washed with hot water (150 ml.), and the combined filtrate and extracts treated with ammonium carbonate (23 g.). After the mixture had been boiled for a few minutes, the precipitated barium carbonate was removed and washed with a little hot water, and the liquor then evaporated to dryness under reduced pressure. The residue was slurried with hot absolute alcohol, the mixture cooled and filtered, and the methionine washed with alcohol and ether (yield 33·8 g.). The alkaline mother-liquors, on treatment with acetic acid (to pH 6), yielded more methionine (3·1 g.) (total yield, 82·6%). The combined crops were recrystallised from water to yield pure methionine (34·0 g.), m. p. 260° (decomp.) [control, 260° (decomp.)]. From the mother-liquors there was obtained somewhat less pure methionine (1·3 g.), m. p. 246° (decomp.) [control, m. p. 249° (decomp.)].

(e) *Hydrolysis of methionine hydantoin with lime.* A mixture of 5-2′-methylthioethylhydantoin (7 g.) and calcium hydroxide (10·0 g.) in water (30 ml.) was heated in an autoclave for 4 hours at 150°. The product was worked up essentially as described under (d) to yield practically pure methionine (4·55 g.; 76%), m. p. 270° (decomp.) [control, m. p. 272° (decomp.)].

When the hydantoin (10 g.) was refluxed with calcium hydroxide (20 g.) and water (200 ml.) for 48 hours, 5·68 g. (66·3%) of methionine were obtained. The residual gum from this preparation was dissolved in a little hot water, and the solution cooled and adjusted to pH 1; some γ-methylthio-α-ureidobutyric acid (0·85 g.) separated on refrigeration; it had m. p. 134—136° (decomp.), not depressed on admixture with the compound prepared from methionine and sodium cyanate.

(f) *Hydrolysis of the urea* (VII; R = H) *with lime.* A mixture of the urea (1 g.), calcium hydroxide (2 g.), and water (20 ml.) was heated in a sealed tube at 150° for 6 hours. The product when worked up as described under (e) gave methionine (0·57 g.).

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655. *Steroids. Part III.** 11-*Oxygenated Steroids from* 22 : 23-*Dibromoergosta*-7 : 9(11)-*dien*-3β-*yl Acetate* (*Ergosteryl-D Acetate* 22 : 23-*Dibromide*).

By Richard Budziarek, Francis Johnson, and F. S. Spring.

Oxidation of ergosteryl-D acetate 22 : 23-dibromide (I) with perbenzoic acid gives 22 : 23-dibromo-9α : 11α-epoxyergost-7-en-3β-yl acetate (II; R = $C_9H_{17}Br_2$), treatment of which with sulphuric acid gives 22 : 23-dibromo-7ξ : 11α-dihydroxyergost-8-en-3β-yl acetate (III; R = $C_9H_{17}Br_2$, R′ = H). Oxidation of the last compound yields 22 : 23-dibromo-7 : 11-diketoergost-8-en-3β-yl acetate (IV; R = $C_9H_{17}Br_2$) and 22 : 23-dibromo-8α : 9α-epoxy-7 : 11-diketoergostan-3β-yl acetate (V; R = $C_9H_{17}Br_2$), treatment of which with zinc gives in each case 7 : 11-diketoergost-22-en-3β-yl acetate (VI; R = C_9H_{17}). 22 : 23-Dibromo-9α : 11α-epoxyergost-7-en-3β-yl acetate (II; R = $C_9H_{17}Br_2$) has been rearranged to 3β-acetoxy-22 : 23-dibromoergost-8-en-7-one (VII; R = $C_9H_{17}Br_2$) by treatment with dilute hydrochloric acid and to 3β-acetoxy-22 : 23-dibromoergost-8-en-11-one (VIII; R = $C_9H_{17}Br_2$) by treatment with boron trifluoride.

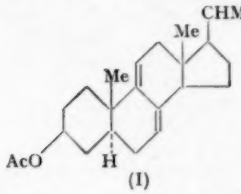
Recent communications from this Laboratory (Anderson, Budziarek, Newbold, Stevenson, and Spring, *Chem. and Ind.*, 1951, 1035; Anderson, Stevenson, and Spring, *J.*, 1952, 2901) described 22 : 23-dibromoergosta-7 : 9(11)-dien-3β-yl acetate (ergosteryl-D acetate 22 : 23-dibromide) (I), its conversion into 7 : 11-diketoergost-22-en-3β-yl acetate (VI; R = C_9H_{17}), and preparation of the last compound directly from ergosteryl-D acetate (Budziarek, Newbold, Stevenson, and Spring, *J.*, 1952, 2892). This paper describes alternative routes to 7 : 11-diketoergost-22-en-3β-yl acetate (VI; R = C_9H_{17}) starting from ergosteryl-D acetate 22 : 23-dibromide (I).

Oxidation of ergosteryl-D acetate 22 : 23-dibromide (I) with one molecular proportion of perbenzoic acid gives a monoepoxide in 70% yield. The reactions of this compound, which are described below, show that it is the 22 : 23-dibromide of ergosteryl-D acetate epoxide, itself obtained by similar oxidation of ergosteryl-D acetate (Chamberlin, Ruyle, Erickson, Chemerda, Aliminosa, Erickson, Sita, and Tishler, *J. Amer. Chem. Soc.*, 1951, **73**, 2396) to which the structure 9α : 11α-epoxyergosta-7 : 22-dien-3β-yl acetate (II; R = C_9H_{17}) was ascribed by Heusser, Eichenberger, Kurath, Dällenbach, and Jeger (*Helv. Chim. Acta*, 1951, **34**, 2106; cf. Budziarek, Newbold, Stevenson, and Spring, *loc. cit.*). An unpublished observation made in this laboratory is that catalytic hydrogenation of ergosteryl-D acetate 22 : 23-dibromide leads to initial saturation of the 9 : 11-ethylenic linkage with formation of 22 : 23-dibromoergost-7-en-3β-yl acetate, which leads us to the view that the monoepoxide of ergosteryl-D acetate 22 : 23-dibromide is likewise formed by saturation of the 9 : 11-ethylenic linkage and is therefore 22 : 23-dibromo-9α : 11α-epoxyergost-7-en-3β-yl acetate (II; R = $C_9H_{17}Br_2$).

Controlled treatment of 22 : 23-dibromo-9α : 11α-epoxyergost-7-en-3β-yl acetate with sulphuric acid in dioxan gives 22 : 23-dibromo-7ξ : 11α-dihydroxyergost-8-en-3β-yl acetate (III; R = $C_9H_{17}Br_2$, R′ = H) in excellent yield. The latter compound is also obtained by treatment of 9α : 11α-epoxyergosta-7 : 22-dien-3β-yl acetate (II; R = C_9H_{17}) in chloroform with bromine. It is readily acetylated to give 3β : 7ξ : 11α-triacetoxy-22 : 23-dibromoergost-8-ene (III; R = $C_9H_{17}Br_2$, R′ = Ac), debromination of which with zinc dust yields 3β : 7ξ : 11α-triacetoxyergosta-8 : 22-diene (III; R = C_9H_{17}, R′ = Ac) identical with a specimen prepared by acetylation of 7ξ : 11α-dihydroxyergosta-8 : 22-dien-3β-yl acetate (III; R = C_9H_{17}, R′ = H) obtained from 9α : 11α-epoxyergosta-7 : 22-dien-3β-yl acetate (II; R = C_9H_{17}) (Chamberlin *et al.*, *loc. cit.*). The triacetate (III; R = C_9H_{17}, R′ = Ac) has recently been obtained by the last route by Heusser, Anliker, Eichenberger, and Jeger (*Helv. Chim. Acta*, 1952, **35**, 936). Debromination of 22 : 23-dibromo-7ξ : 11α-dihydroxyergost-8-en-3β-yl acetate (III; R = $C_9H_{17}Br_2$, R′ = H) with zinc gives 7ξ : 11α-dihydroxyergosta-8 : 22-dien-3β-yl acetate (III; R = C_9H_{17}, R′ = H) in excellent yield.

* Part II, *J.*, 1952, 2901.

Oxidation of 22 : 23-dibromo-7ξ : 11α-dihydroxyergost-8-en-3β-yl acetate (III; $R = C_9H_{17}Br_2$, $R' = H$) with chromic acid gives a mixture of 22 : 23-dibromo-7 : 11-diketoergost-8-en-3β-yl acetate (IV; $R = C_9H_{17}Br_2$) and 22 : 23-dibromo-8α : 9α-epoxy-7 : 11-diketoergostan-3β-yl acetate (V; $R = C_9H_{17}Br_2$). This parallels the similar oxidation of 7ξ : 11α-dihydroxyergosta-8 : 22-dien-3β-yl acetate (III; $R = C_9H_{17}$, $R' = H$)



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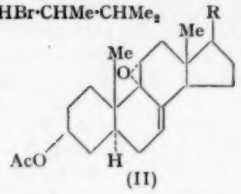

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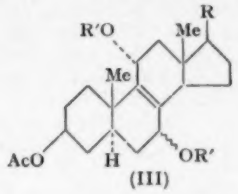

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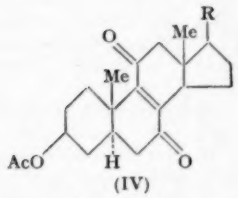
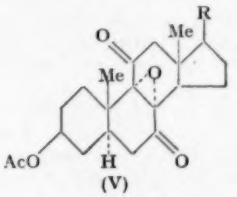
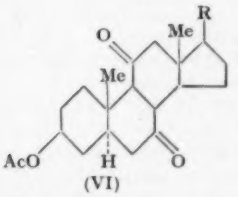


(IV)



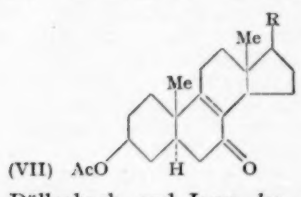
(V)



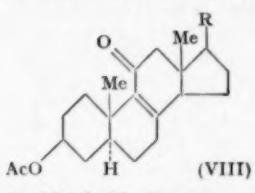
(VI)

(Heusser *et. al., loc. cit.*, 1951) to 7 : 11-diketoergosta-8 : 22-dien-3β-yl acetate (IV; $R = C_9H_{17}$) and 8α : 9α-epoxy-7 : 11-diketoergost-22-en-3β-yl acetate (V; $R = C_9H_{17}$). Treatment of (IV; $R = C_9H_{17}Br_2$) or (V; $R = C_9H_{17}Br_2$) with zinc dust in acetic acid gives 7 : 11-diketoergost-22-en-3β-yl acetate (VI; $R = C_9H_{17}$). 22 : 23-Dibromo-7 : 11-diketoergost-8-en-3β-yl acetate (IV; $R = C_9H_{17}Br_2$) was also obtained in poor yield by oxidation of 22 : 23-dibromo-9α : 11α-epoxyergost-7-en-3β-yl acetate (II; $R = C_9H_{17}Br_2$) with chromic acid.

Treatment of 22 : 23-dibromo-9α : 11α-epoxyergost-7-en-3β-yl acetate (II; $R = C_9H_{17}Br_2$) with aqueous hydrochloric acid, followed by acetylation of the product, gives 3β-acetoxy-22 : 23-dibromoergost-8-en-7-one (VII; $R = C_9H_{17}Br_2$), debromination of which with zinc gives the known 3β-acetoxyergosta-8 : 22-dien-7-one (VII; $R = C_9H_{17}$) (Stavely and Bollenback, *J. Amer. Chem. Soc.*, 1943, **65**, 1290; Heusser, Eichenberger,



(VII)



(VIII)

Kurath, Dällenbach, and Jeger, *loc. cit.*; Budziarek, Newbold, Stevenson, and Spring, *loc. cit.*). 3β-Acetoxy-22 : 23-dibromoergost-8-en-11-one (VIII; $R = C_9H_{17}Br_2$) was obtained by treatment of 22 : 23-dibromo-9α : 11α-epoxyergost-7-en-3β-yl acetate (II; $R = C_9H_{17}Br_2$) with boron trifluoride, using the method described by Heusser *et al.* (*loc. cit.*) for the preparation of 3β-acetoxyergosta-8 : 22-dien-11-one (VIII; $R = C_9H_{17}$). The compound (VIII; $R = C_9H_{17}$) was obtained in excellent yield by debromination of (VIII; $R = C_9H_{17}Br_2$) with zinc.

Experimental

M. p.s are corrected. Specific rotations were determined on chloroform solutions (unless otherwise stated) in a 1-dm. tube at approx. 15°. Ultra-violet absorption spectra were measured on ethanol solutions, with a Unicam SP.500 spectrophotometer. For chromatography, activated alumina, Grade II, standardised according to Brockmann, was employed.

22 : 23-*Dibromo*-9α : 11α-*epoxyergost*-7-*en*-3β-*yl Acetate*.—Ergosteryl-D acetate 22 : 23-di-

bromide (2 g.) in chloroform (50 c.c.) was treated dropwise with perbenzoic acid (1·2 mols.) in chloroform (10 c.c.), added with stirring during 3 hours at 0°. The mixture was kept at 0° for a further 2 hours. The solution was concentrated under reduced pressure until solid separated, whereafter the mixture was diluted with ether (50 c.c.). The solution was shaken successively with 5% sodium carbonate solution and water and dried ($MgSO_4$). The solid (2 g.), obtained by removal of the solvents at 30—40° under reduced pressure, crystallised from pure acetone or from light petroleum (b. p. 40—60°), to give 22 : 23-*dibromo*-9α : 11α-*epoxyergost*-7-*en*-3β-*yl acetate* as flat needles, m. p. 218°, $[\alpha]_D$ −24°, −26° (*c*, 1·5, 1·7) (Found: C, 58·5; H, 7·6. $C_{30}H_{46}O_3Br_2$ requires C 58·6; H, 7·55%). It gives a yellow colour with tetranitromethane in chloroform and does not show selective absorption of high intensity above 2200 Å. Attempted crystallisation of the epoxide from technical acetone or methanol caused rearrangement.

22 : 23-*Dibromo*-9α : 11α-*epoxyergost*-7-*en*-3β-*ol*.—A solution of 22 : 23-dibromo-9α : 11α-epoxyergost-7-en-3β-ylacetate (300 mg.) in benzene (50 c.c.) and methanolic potassium hydroxide (50 c.c.; 2%) was refluxed for 2 hours. Precipitation with water and isolation by means of ether gave a product which after three crystallisations from methanol gave 22 : 23-*dibromo*-9α : 11α-*epoxyergost*-7-*en*-3β-*ol* as plates, m. p. 200—202° (260 mg.), $[\alpha]_D$ −27° (*c*, 0·7) (Found: C, 58·0; H, 8·0. $C_{28}H_{44}O_2Br_2,CH_3{\cdot}OH$ requires C, 57·6; H, 8·0%). It gives a yellow colour with tetranitromethane in chloroform and does not show selective absorption of high intensity above 2200 Å.

22 : 23-*Dibromo*-7ξ : 11α-*dihydroxyergost*-8-*en*-3β-*yl Acetate*.—(*a*) Powdered 22 : 23-dibromo-9α : 11α-epoxyergost-7-en-3β-yl acetate (600 mg.) was shaken vigorously in dioxan (50 c.c.) containing aqueous sulphuric acid 2N; 10 c.c.). After a few seconds solution was complete and almost immediately solid separated. After 15 minutes the crystalline solid was filtered off and washed successively with methanol, water, methanol, and ether (small prisms, m. p. 204°; 420 mg.). Two crystallisations from pyridine gave 22 : 23-*dibromo*-7ξ : 11α-*dihydroxyergost*-8-*en*-3β-*yl acetate* as needles, m. p. 216—217°, $[\alpha]_D$ +93° (*c*, 0·3 in pyridine) (Found: C, 56·8; H, 7·8. $C_{30}H_{48}O_4Br_2$ requires C, 57·0; H, 7·65%). It does not show selective absorption of high intensity above 2200 Å; it is very sparingly soluble in most organic solvents including chloroform.

Attempted crystallisation of the dibromo-epoxide from technical acetone led to the separation of a microcrystalline solid, m. p. 200°, which is very insoluble in most organic solvents, including chloroform, and is undepressed in m. p. when mixed with 22 : 23-dibromo-7ξ : 11α-dihydroxyergost-8-en-3β-yl acetate, m. p. 204° (Found: C, 56·6; H, 8·0.

(*b*) 9α : 11α-Epoxyergosta-7 : 22-dien-3β-yl acetate (200 mg.) in chloroform (10 c.c.) was treated dropwise with a solution of bromine (1 mol.) in chloroform during 20 minutes at −4°. The solution was kept overnight at −5°. Chloroform was removed under reduced pressure at room temperature. The residue separated from acetone as a microcrystalline powder (100 mg.), very insoluble in most organic solvents including chloroform, and has m. p. 200°, undepressed when mixed with 22 : 23-dibromo-7ξ : 11α-dihydroxyergost-8-en-3β-yl acetate, m. p. 204°.

3β : 7ξ : 11α-*Triacetoxy*-22 : 23-*dibromoergost*-8-*ene*.—A suspension of 22 : 23-dibromo-7ξ : 11α-dihydroxyergost-8-en-3β-yl acetate (400 mg.) in pyridine (15 c.c.) and acetic anhydride (15 c.c.) was heated on the steam-bath for 30 minutes, after which solution was complete; the solution was kept overnight at room temperature. Most of the solvents were removed under reduced pressure at 60—80°, the residue was diluted with water, and the product isolated by means of ether. Crystallisation from methanol gave 3β : 7ξ : 11α-*triacetoxy*-22 : 23-*dibromoergost*-8-*ene* as prisms, m. p. 171—172° (350 mg.), $[\alpha]_D$ +77° (*c*, 1·9) (Found: C, 56·8; H, 7·5. $C_{34}H_{52}O_6Br_2$ requires C, 57·0; H, 7·3%). It gives a pale yellow colour with tetranitromethane in chloroform and does not show selective absorption of high intensity above 2200 Å.

3β : 7ξ : 11α-*Triacetoxyergosta*-8 : 22-*diene*.—(*a*) A solution of 3β : 7ξ : 11α-triacetoxy-22 : 23-dibromoergost-8-ene (100 mg.) in ether–methanol (30 c.c.; 1 : 1) was refluxed for 3 hours with zinc dust (2 g.) added portionwise. After filtration, water was added and the product isolated by means of ether. Crystallisation from methanol gave 3β : 7ξ : 11α-triacetoxyergosta-8 : 22-diene as prismatic needles, m. p. 172° (90 mg.), $[\alpha]_D$ +88° (*c*, 1·2) (Found: C, 73·5; H, 9·6. Calc. for $C_{34}H_{52}O_6$: C, 73·3; H, 9·4%). Heusser, Anliker, Eichenberger, and Jeger (*loc. cit.*) give m. p. 170—171°, $[\alpha]_D$ +92°. It gives a pale yellow colour with tetranitromethane in chloroform and does not exhibit selective absorption of high intensity above 2200 Å.

(*b*) Acetylation of 7ξ : 11α-dihydroxyergost-8-en-3β-yl acetate on the steam-bath for 1 hour with acetic anhydride and pyridine gave 3β : 7ξ : 11α-triacetoxyergosta-8 : 22-diene which separated from methanol as prismatic needles, $[\alpha]_D$ +90° (*c*, 2·0), m. p. 172—173°, undepressed in m. p. when mixed with a specimen prepared as described above (Found: C, 72·9; H, 9·4%).

7ξ : 11α-*Dihydroxyergosta*-8 : 22-*dien*-3β-*yl Acetate*.—A solution of 22 : 23-dibromo-7ξ : 11α-dihydroxyergost-8-en-3β-yl acetate (m. p. 204°; 200 mg.) in pyridine (30 c.c.) containing water (3 drops) was heated with zinc dust (2 g.) for 3 hours on the steam-bath. The mixture was filtered and the filtrate evaporated to dryness under reduced pressure. The residue separated from acetone in felted needles, m. p. 231—234° (150 mg.), which on recrystallisation from methanol separated as prismatic needles, m. p. 251—253°, $[\alpha]_D$ +85° (*c*, 0·4), identical with a specimen obtained by the treatment of ergosteryl-D acetate epoxide with sulphuric acid in dioxan (m. p. 230—232°, $[\alpha]_D$ +83° from acetone; m. p. 248—250° from methanol). It gives a pale yellow colour with tetranitromethane in chloroform and does not exhibit selective absorption of high intensity above 2200 Å (Found: C, 76·6; H, 10·5. Calc. for $C_{30}H_{46}O_4$: C, 76·2; H, 10·2%). Chamberlin, Ruyle, Erickson, Chemerda, Aliminosa, Erickson, Sita, and Tishler (*loc. cit.*) give m. p. 248—252°, $[\alpha]_D$ +85°, and Heusser, Eichenberger, Kurath, Dällenbach, and Jeger (*loc. cit.*) give m. p. 270—272°, $[\alpha]_D$ +82°.

22 : 23-*Dibromo*-8α : 9α-*epoxy*-7 : 11-*diketoergostan*-3β-*yl Acetate*.—A suspension of 22 : 23-dibromo-7ξ : 11α-dihydroxyergost-8-en-3β-yl acetate (m. p. 204°; 3·6 g.) in acetic acid (400 c.c.) was treated portionwise with a solution of chromic anhydride in acetic acid (1·05N; 2·5 g.-atoms of oxygen), and the mixture stirred for 2 hours at room temperature and then kept overnight. After addition of a little methanol, the solution was concentrated under reduced pressure and diluted with water. The product, isolated by means of ether, separated from methanol–chloroform as plates (1·7 g.), m. p. 240°. A solution of this solid in benzene (100 c.c.) was chromatographed on activated alumina (2 × 8 cm.). Evaporation of the first benzene fraction (300 c.c.) gave a solid (200 mg.) which after crystallisation from methanol gave 22 : 23-*dibromo*-8α : 9α-*epoxy*-7 : 11-*diketoergostan*-3β-*yl acetate* as flat needles, m. p. 210—212°, $[\alpha]_D$ −44° (*c*, 1·8) (Found: C, 56·2; H, 7·2. $C_{30}H_{44}O_5Br_2$ requires C, 55·9; H, 6·9%). It gives no colour with tetranitromethane in chloroform and does not show selective absorption of high intensity above 2000 Å.

22 : 23-*Dibromo*-7 : 11-*diketoergost*-8-*en*-3β-*yl Acetate*.—(*a*) Evaporation of the second benzene fraction (500 c.c.) from the above chromatogram gave 22 : 23-*dibromo*-7 : 11-*diketoergost*-8-*en*-3β-*yl acetate* (600 mg.), separating from methanol–chloroform as hexagonal plates, m. p. 250—251°, $[\alpha]_D$ +27°, +24° (*c*, 1·9, 0·9) (Found: C, 57·2; H, 7·25. $C_{30}H_{44}O_4Br_2$ requires C, 57·3; H, 7·05%). Light absorption: Maximum at 2690 Å (ε = 8200). It does not give a colour with tetranitromethane in chloroform.

(*b*) A solution of 22 : 23-dibromo-9α : 11α-epoxyergost-7-en-3β-yl acetate (2 g.) in acetic acid (170 c.c.) was treated dropwise with a solution of chromic anhydride in acetic acid (1·05N; 4 atomic equivs. of oxygen) during 1 hour at 50° with stirring. The mixture was stirred for an additional hour at 50°, cooled to room temperature, and diluted with water. Isolation by means of ether gave a yellow solid, a solution of which in light petroleum (b. p. 60—80°)–benzene (10 : 1; 100 c.c.) was chromatographed on activated alumina (2 × 12 cm.). Elution with light petroleum–benzene (4 : 1; 400 c.c.) gave a solid *substance* (450 mg.) which crystallised from methanol in blades, m. p. 218—219°, $[\alpha]_D$ +100°, +101° (*c*, 1·4, 1·0). Light absorption: Maximum at 2460 Å (ε = 9000) (Found: C, 57·1; H, 7·3. $C_{30}H_{46}O_4Br_2$ requires C, 57·1; H, 7·35. $C_{30}H_{44}O_4Br_2$ requires C, 57·3; H, 7·05%). Evaporation of the next light petroleum–benzene (3 : 2; 400 c.c.) fraction gave a solid (100 mg.) which on crystallisation from methanol gave 22 : 23-dibromo-7 : 11-diketoergost-8-en-3β-yl acetate as plates, m. p. 248°, $[\alpha]_D$ +20° (*c*, 0·5) (Found: C, 57·0; H, 7·2%). Light absorption: Maximum at 2680 Å (ε = 8000); it showed no depression of the m. p. when mixed with the specimen described above.

7 : 11-*Diketoergost*-22-*en*-3β-*yl Acetate*.—(*a*) A solution of 22 : 23-dibromo-7 : 11-diketoergost-8-en-3β-yl acetate (50 mg.) in glacial acetic acid (25 c.c.) was heated on the steam bath for 3 hours with zinc dust (1 g.) and then boiled under reflux for 15 minutes. Isolation of the product with ether gave 7 : 11-diketoergost-22-en-3β-yl acetate (30 mg.) as needles (from methanol), m. p. 195—196°, $[\alpha]_D$ −26° (*c*, 0·4) (Found: C, 76·4; H, 10·0. Calc. for $C_{30}H_{46}O_4$: C, 76·55; H, 9·85%); It is undepressed in m. p. when mixed with an authentic specimen prepared as described by Budziarek *et al.* (*loc. cit.*). It gives a faint yellow colour with tetranitromethane in chloroform and does not show high intensity light absorption above 2200 Å.

(*b*) Similar reduction of 22 : 23-dibromo-8α : 9α-epoxy-7 : 11-diketoergostan-3β-yl acetate (100 mg.) with zinc dust and acetic acid gave a product isolated by means of ether. A solution of this product in benzene (20 c.c.) was filtered through a column of alumina (5 × 1 cm.), and the column washed with benzene (250 c.c.). Evaporation of the benzene filtrate gave 7 : 11-diketoergost-22-en-3β-yl acetate (60 mg.), m. p. 197—198°, $[\alpha]_D$ −28° (*c*, 1·2); it is undepressed in m. p. when mixed with the specimen described under (*a*).

3β-*Acetoxy*-22 : 23-*dibromoergost*-8-*en*-7-*one*.—A solution of 22 : 23-dibromo-9α : 11α-epoxyer-

gost-7-en-3β-yl acetate (700 mg.) in benzene (7 c.c.) was refluxed with aqueous methanolic hydrochloric acid (100 c.c.; 1%) for 1½ hours. A solution of the product, isolated in the usual manner, in pyridine (15 c.c.) was heated with acetic anhydride (10 c.c.) for 4 hours at 100°. The acetylated product (m. p. 233°; 120 mg.), isolated by means of ether, was purified by filtration of its solution in benzene (10 c.c.) through a short column of activated alumina. Elution with the same solvent gave 3β-*acetoxy*-22 : 23-*dibromoergost*-8-*en*-7-*one* which crystallised from methanol in plates, m. p. 241—242°, $[\alpha]_D$ −29° (*c*, 1·5) (Found : C, 58·6; H, 7·6. $C_{30}H_{46}O_3Br_2$ requires C, 58·6; H, 7·55%). Light absorption : Maximum at 2520 Å (ε = 10,000). It does not give a colour with tetranitromethane in chloroform.

3β-*Acetoxyergosta*-8 : 22-*dien*-7-*one*.—A solution of 3β-acetoxy-22 : 23-dibromoergost-8-en-7-one (50 mg.) in ether–ethanol (40 c.c.; 1 : 1) was refluxed for 2 hours with zinc dust (1 g.), added portionwise. After filtration, the solution was concentrated and poured into water. Isolation by means of ether gave a solid which crystallised from methanol to yield 3β-acetoxyergosta-8 : 22-dien-7-one as plates, m. p. 209—211°, $[\alpha]_D$ −56° (*c*, 0·5) (Found : C, 79·3; H, 10·3. Calc. for $C_{30}H_{46}O_3$: C, 79·2; H, 10·2%); it is undepressed in m. p. when mixed with an authentic specimen. Light absorption : Maximum at 2520 Å (ε = 10,000). It gives a yellow colour with tetranitromethane in chloroform.

3β-*Acetoxy*-22 : 23-*dibromoergost*-8-*en*-11-*one*.—(*a*) A solution of 22 : 23-dibromo-9α : 11α-epoxyergost-7-en-3β-yl acetate (1 g.) in dry benzene (50 c.c.) was treated with redistilled boron trifluoride–ether complex (15 drops) and the solution kept at room temperature for 3 days. The solution was diluted with ether (50 c.c.), washed successively with water, sodium hydrogen carbonate solution, and water, and dried (Na_2SO_4). The solvents were removed under reduced pressure; the residue separated from methanol–chloroform in elongated plates, m. p. 190° (0·73 g.). Light absorption : Maximum at 2530 Å (ε = 9100). A solution of the solid in benzene (25 c.c.) was filtered through a short column of activated alumina, and the column washed with the same solvent. Evaporation of the filtrate gave 3β-*acetoxy*-22 : 23-*dibromoergost*-8-*en*-11-*one* which separated from methanol–chloroform in blades, m. p. 201—202°, $[\alpha]_D$ +98° (*c*, 1·7) (Found : C, 58·7; H, 7·7. $C_{30}H_{46}O_3Br_2$ requires C, 58·6; H, 7·55%). Light absorption : Maximum at 2530 Å (ε = 9800 . It does not give a colour with tetranitromethane in chloroform.

(*b*) 3β Acetoxyergosta-8 : 22-dien-11-one (100 mg.) in chloroform (10 c.c.) was treated with a solution of bromine (1 mol.) in chloroform, added dropwise during 20 minutes with stirring at 0°. The colourless solution was kept overnight at −4°, diluted with chloroform (50 c.c.), washed with sodium hydrogen carbonate solution and water, and dried (Na_2SO_4). A solution of the solid obtained by removal of the ether, in light petroleum (b. p. 60—80°)–benzene (7 : 3; 50 c.c.), was filtered through a column of activated alumina (2 × 10 cm.). Elution of the column with the same solvent gave a fraction, m. p. 194—195° (50 mg.), which crystallised from methanol, to give 3β-acetoxy-22 : 23-dibromoergost-8-en-11-one as plates, m. p. 200—201°, $[\alpha]_D$ +99° (*c*, 1·0) (Found : C, 58·4; H, 7·6%). Light absorption : Maximum at 2530 Å (ε = 9000). A mixture with a specimen described under (*a*) had m. p. 200—201°.

3β-*Acetoxyergosta*-8 : 22-*dien*-11-*one*.—A solution of 3β-acetoxy-22 : 23-dibromoergost-8-en-11-one (300 mg.) in ether (60 c.c.) and methanol (60 c.c.) was refluxed for 2 hours with zinc dust (3 g.), added portionwise. The mixture was filtered, the filtrate concentrated under reduced pressure, and the crystalline solid (m. p. 120—130°; 200 mg.) separating collected and thrice crystallised from methanol, to give 3β-acetoxy-8 : 22-dien-11-one as elongated plates, m. p. 129—131°, $[\alpha]_D$ +105°, +102° (*c*, 1·6, 0·9) (Found : C, 79·2; H, 10·2. Calc. for $C_{30}H_{46}O_3$: C, 79·2; H, 10·2%); it is undepressed in m. p. when mixed with an authentic specimen, m. p. 129—130°, $[\alpha]_D$ +102°, prepared according to Heusser *et al.* (*loc. cit.*) who give m. p. 122—123°, $[\alpha]_D$ +92°. Light absorption : Maximum at 2540 Å (ε = 9600).

We thank Dr. G. T. Newbold and Mr. Duncan Maclean, B.Sc., for assistance. Microanalyses were by Dr. A. C. Syme and Mr. Wm. McCorkindale.

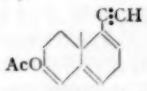
The Royal Technical College, Glasgow, C.1. [*Received, May 13th*, 1952.]

656. *Some Reactions of* 3-*Methyl*cyclo*pent*-2-*enone*.

By R. M. Acheson.

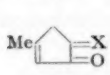
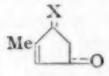
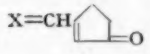
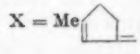
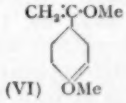
Neither 3-methyl*cyclo*pent-2-enone nor methyl 4-keto-2-methyl*cyclo*pent-2-ene-1-carboxylate appears to undergo the Diels–Alder reaction. 3-Methyl*cyclo*pent-2-enone reacts with benzaldehyde to give a mixture of α-(4-keto-2-methyl*cyclo*pent-2-enyl)benzyl alcohol and 3-styryl*cyclo*pent-2-enone.

A number of *cyclo*pent-2-enone derivatives, including *cyclo*pent-2-enone itself, 5 : 5-dibromo*cyclo*pent-2-ene-1 : 4-dione, and 2-methyl*cyclo*pent-2-ene-1 : 5-dione (Dane *et al.*, *Annalen*, 1939, **537**, 246 and earlier papers), 2-methyl- (Bockemüller, U.S.P. 2,179,809; Gaddis and Butz, *J. Amer. Chem. Soc.*, 1947, **69**, 1203), and 2 : 4-dimethyl*cyclo*pent-2-enone (Nazarov and Bergel'son, *Zhur. Obschei Chim.*, 1950, **20**, 648) have been successfully used in the Diels–Alder synthesis of sterol derivatives containing the intact D ring. It was therefore hoped to build up the sterol ring system by this reaction from 3-methyl-*cyclo*pent-2-enone derivatives (*e.g.*, II) by reaction with dienes of the 3 : 7 : 8 : 9-tetrahydro-1-vinyl- or 3 : 7 : 8 : 9-tetrahydro-1-ethynyl-naphthalene type (*e.g.*, I) (Acheson and Robinson, *J.*, 1952, 1127).

(I)  (II)

Towards this end 3-methyl*cyclo*pent-2-enone (Acheson and Robinson, *loc. cit.*) was heated with 2-methoxybutadiene and a trace of pyrogallol at 200° for 24 hours; the addition of a little diethylamine or diethylaniline did not alter the course of the reaction which yielded small quantities of a colourless solid, and an oil which gave a yellow derivative with 2 : 4-dinitrophenylhydrazine in methanolic sulphuric acid.

The solid did not react with 2 : 4-dinitrophenylhydrazine or semicarbazide although its infra-red absorption spectrum indicated the presence of a highly conjugated carbonyl group. It is almost certainly 3-methyl-4-(3-methyl*cyclo*pent-2-enylidene)*cyclo*pent-2-enone (IV) formed by the self-condensation of the 3-methyl*cyclo*pent-2-enone. Its ultra violet absorption [max. at 2550 (ε 8900) and 3250 Å (ε 19,050) in methanol] is more in accord with (IV) than with the isomeric (III), and (IV) is analogous to one of the products

 (III)  (IV)  (V)   (VI)

obtained from 3-methyl*cyclo*pent-2-enone and benzaldehyde (see below). The third possibility, (V), is excluded as Kuhn–Röth determination indicated the presence of more than one *C*-methyl group in the molecule. A similar self-condensation product, 2-*cyclo*-pentylidene*cyclo*pentanone, has been obtained from *cyclo*pentanone and sodium ethoxide (Wallach, *Ber.*, 1896, **29**, 2955).

The oily product is almost certainly 1-methoxy-4-1'-methoxyvinyl*cyclo*hexene (VI), which has been prepared by heating 2-methoxybutadiene with pyrogallol at 180—190° (Nazarov, Verkholetova, and Bergel'son, *Izvest. Akad. Nauk. S.S.S.R., Otdel. Khim. Nauk.*, 1948, 511) and is easily hydrolysed by dilute acid to 4-acetyl*cyclo*hexanone. The yellow 2 : 4-dinitrophenylhydrazone appears to be the bis-derivative of this diketone.

Attempts to effect a Diels–Alder condensation between methyl 4-keto-2-methyl*cyclo*-pent-2-ene-1-carboxylate, prepared from the corresponding acid (Acheson and Robinson, *loc. cit.*) with diazomethane, and *cyclo*pentadiene in the presence of a trace of pyrogallol, with or without trimethylamine or trichloroacetic acid, at room temperature or at 40° were unsuccessful. *cyclo*Pentadiene similarly failed to react with 3-methyl*cyclo*pent-2-enone.

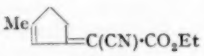
An attempt to condense 6-acetoxy-1-ethynyl-3 : 7 : 8 : 9-tetrahydro-9-methylnaph-

thalene (I) (Friedmann and Robinson, unpublished) with methyl 4-keto-2-methyl*cyclo*pent-2-ene-1-carboxylate (II) in the presence of a trace of pyrogallol at 155—165° for 7 hours under nitrogen gave unchanged material and small quantities of yellow gums which had no appreciable ultra-violet absorption in the region of 2750 Å. Thus little, if any, material was present containing the *cyclo*hexa-1 : 3-diene system which must be formed in a normal Diels–Alder reaction. The infra-red absorption spectra indicated that the gums were complex mixtures.

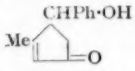
It is of interest that none of the *cyclo*pent-2-enones which undergo the Diels–Alder reaction have a methyl group in position 3, and that the introduction of a methyl group in the β-position of an αβ-unsaturated ketone which undergoes the reaction almost always reduces the yield (cf. Table V, listing Diels–Alder reactions, in "Organic Reactions," Vol. IV, p. 96).

In order to see whether any cationoid activity was exhibited at position 3 in 3-methyl*cyclo*pent-2-enone this compound was treated with cold ethyl sodiocyanoacetate. None of the Michael addition product could be isolated, but ethyl α-cyano-3-methyl*cyclo*pent-2-enylideneacetate (VII) was obtained in good yield. This was stable to boiling concentrated hydrochloric acid (3 hours), and reacted slowly with bromine in hot carbon tetrachloride.

Benzaldehyde and 3-methyl*cyclo*pent-2-enone in the presence of aqueous sodium hydroxide (cf. *Org. Synth.*, Coll. Vol. 1, 1932, p. 69) gave α-(4-keto-2-methyl*cyclo*pent-2-enyl)benzyl alcohol (VIII) and a small proportion of 3-styryl*cyclo*pent-2-enone (characterised as its bright red 2 : 4-dinitrophenylhydrazone) which were separated on alumina.

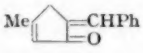


(VII)



(VIII)

(IX)



(X)

The alcohol (VIII) was dehydrated to 4-benzylidene-3-methyl*cyclo*pent-2-enone (IX) by acidic reagents, and also lost water in the presence of 2 : 4-dinitrophenylhydrazine in methanolic sulphuric acid to give the dull red 2 : 4-dinitrophenylhydrazone of (IX) which was also prepared directly therefrom. The second condensation product contained no *C*-methyl group and must therefore have the structure stated, which is confirmed by the similarity of its absorption spectrum [max. at 2400 (ε 8600) and 3200 Å (ε 39,000) in methanol] with that of 6-phenylhexa-3 : 5-dien-2-one [max. at 2340 (ε 6760) and 3190 Å (ε 36,300); Wilds, Beck, Close, Djerassi, Johnson, Johnson, and Shunk, *J. Amer. Chem. Soc.*, 1947, **69**, 1993). The absorption spectrum of its 2 : 4-dinitrophenylhydrazone is also consistent with this structure [max. at 4200 Å (ε 38,700) in chloroform; octatrienal 2 : 4-dinitrophenylhydrazone, 4100 Å (ε 36,500) (Braude and Jones, *J.*, 1945, 498)].

The isomeric ketone, obtained by dehydration of the alcohol, contained one *C*-methyl group and must therefore be (IX) or (X). According to its absorption spectrum [max. at 2300 (ε 11,300) and 3000 Å (ε 18,400) in methanol] it is much less conjugated than 3-styryl*cyclo*pent-2-enone. Unfortunately the absorption spectrum of 5-methyl-1-phenylhexa-1 : 4-dien-3-one, an open-chain analogue (Esafov and Raikher, *J. Gen. Chem., U.S.S.R.*, 1943, **13**, 809), is not available for comparison. The ketone (IX or X) and 3-styryl*cyclo*pent-2-enone exhibit a higher degree of conjugation than benzylideneacetone, which has a maximum at 2860 Å (ε 23,400) (Wilds *et al.*, *loc. cit.*). The absorption of the 2 : 4-dinitrophenylhydrazone of the ketone (IX or X) [max. at 4200 (ε 28,000) in chloroform] is very similar to that of the 3-styryl*cyclo*pentenone derivative which suggests that the conjugation in both ketones is similar and that the ketone in question is therefore (IX). There is however no recorded spectrum for a reference compound similarly conjugated to the 2 : 4-dinitrophenylhydrazone of (IX), and the less conjugated phorone 2 : 4-dinitrophenylhydrazone shows a maximum at 3950 Å (ε 24,500) (Braude and Jones, *loc. cit.*). The ketone is therefore provisionally considered to have structure (IX) which is analogous to that of the 3-methyl*cyclo*pent-2-enone self-condensation product (IV). The parent alcohol is therefore (VIII), but the alternative structures for this and its dehydration product are not excluded. The infra-red absorption spectrum of the alcohol shows that there is no

appreciable interaction between the keto- and the hydroxy-group; this might take place if it had the isomeric structure. The rather short wave-length of the absorption maxima of (IX) in comparison with that of 3-styrylcyclopent-2-enone may be due to stereochemical factors, and a comparison with the absorption of the *cis*- and the *trans*-form of 1-phenylbutadiene [max. at 2650—2690 (ε 18,400) and 2800 Å (ε 29,800) respectively (Grumitt and Christoph, *J. Amer. Chem. Soc.*, 1949, **71**, 4157)] is of interest in this connexion.

3-Methylcyclopent-2-enone reacted vigorously with selenium dioxide in dioxan or glacial acetic acid, to give a product containing selenium. Very little distillable material was formed, and the reaction was not further investigated.

Experimental

Methyl 4-*Keto*-2-*methylcyclopent*-2-*ene*-1-*carboxylate* (II).—4-Keto-2-methylcyclopent-2-ene-1-carboxylic acid (Acheson and Robinson, *loc. cit.*) in methanol on treatment with the theoretical quantity of ethereal diazomethane gave the *methyl* ester, b. p. 112—116°/0·5 mm., n_D^{18} 1·5030 (Found: C, 62·6; H, 6·6. $C_8H_{10}O_3$ requires C, 62·3; H, 6·5%). The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in long orange-red prisms, m. p. 195° (Found: C, 50·6; H, 4·3; N, 16·7. $C_{14}H_{14}O_6N_4$ requires C, 50·3; H, 4·2; N, 16·8%). The *semicarbazone* separated from aqueous methanol in prisms, m. p. 227—228° (decomp.; darkening from *ca.* 200°) (Found: C, 51·3; H, 6·2; N, 19·6. $C_9H_{13}O_3N_3$ requires C, 51·2; H, 6·2; N, 19·9%).

3-*Methylcyclopent*-2-*enone and* 2-*Methoxybutadiene*.—3-Methylcyclopent-2-enone (15·0 g.; purified *via* its semicarbazone), 2-methoxybutadiene (3·3 g.), and pyrogallol (0·07 g.) were kept at 200—215° for 24 hours. Very little methoxybutadiene remained (smell) when the tube was opened. The residual brown liquid on distillation gave unchanged 3-methylcyclopent-2-enone (12·7 g.; n_D^{17} 1·4908), b. p. 69—73°/14 mm., and yellow oils; A, b. p. 120—70°/0·08 mm. (1·0 g.), and B, b. p. 170—200°/0·08 mm (0·75 g.).

Fraction A was chromatographed in light petroleum (b. p. 40—60°; 20 c.c.) on alumina (20 g.). Elution with light petroleum (b. p. 40—60°; 140 c.c.) gave a pale yellow oil C (0·33 g.); pure benzene gave a colourless oil D which partly solidified (0·1 g.); and ethyl acetate gave a thick yellow oil E (0·1 g.). The oil C gave a deep red solid derivative with 2 : 4-dinitrophenylhydrazine in methanolic sulphuric acid. Repeated crystallisation of this derivative from dioxan gave yellow needles of 4-*acetylcyclohexanone bis*-2 : 4-*dinitrophenylhydrazone*, m. p. 205—207° (decomp.) (Found: C, 48·1; H, 4·4; N, 22·0. $C_{20}H_{20}O_8N_8$ requires C, 48·0; H, 4·0; N, 22·4%). No other crystalline material could be isolated from the (first) deep red mother-liquor. The oil D crystallised from water containing a little ethanol, giving colourless prisms of 3-*methyl*-4-(3-*methylcyclopent*-2-*enylidine*)*cyclopent*-2-*enone* (IV), m. p. 126—127° (Found: C, 82·6; H, 8·1; *C*-Me, 14·5. $C_{12}H_{14}O$ requires C, 82·8; H, 8·0; 2*C*-Me, 17·2%). The oil E gave a non-crystalline derivative with 2 : 4-dinitrophenylhydrazine in methanolic sulphuric acid. The oil B was chromatographed in light petroleum (b. p. 60—80°) containing 5% (v/v) of benzene on alumina. The benzene eluate (0·25 g.) was the only one which could be identified. It was largely 3-methyl-4-(3-methylcyclopent-2-enylidene)*cyclo*pent-2-enone which after crystallisation had m. p. 124—127° alone or mixed with a specimen obtained from the first chromatogram.

Ethyl α-*Cyano*-3-*methylcyclopent*-2-*enylideneacetate*.—3-Methylcyclopent-2-enone (9·6 g.) was added to a solution of sodium (4·5 g.) in ethyl cyanoacetate (45·0 g.). After 1 day at room temperature the mixture changed from a yellow sludge in much liquid to an apparently solid red-yellow mass. After 4 days in all the mixture was treated with ether (200 c.c.) and water (75 c.c.) containing concentrated hydrochloric acid (11 c.c.). After filtration from some of the product (2·8 g.), which was later combined with the main portion, the ethereal solution, which was red and had a green fluorescence, was washed with water and dried. The ether and excess of ethyl cyanoacetate were removed *in vacuo*. The residual oil solidified, to give *ethyl* α-*cyano*-3-*methylcyclopent*-2-*enylideneacetate* (11·1 g.; total, 73% crude yield), which crystallised from ethanol in colourless prisms, m. p. 123° (Found: C, 69·1; H, 6·8; N, 7·4. $C_{11}H_{13}O_2N$ requires C, 69·1; H, 6·8; N, 7·3%). Its infra-red absorption spectrum in paraffin paste showed maxima at 4·51 (CN), 5·84 (αβ-unsaturated ester), 6·21 and 6·39 (double bond), 7·83 (ester), and at 11·85 mμ.

3-*Methylcyclopent*-2-*enone and Benzaldehyde*.—A mixture of 3-methylcyclopent-2-enone (10·0 g.), benzaldehyde (5·3 g.), and 10% aqueous sodium hydroxide (1·0 c.c.) was vigorously stirred at room temperature for 18 hours. The mixture became dark brown and was neutralised with dilute hydrochloric acid and extracted with ether, followed by benzene. The mixed

extracts were washed with water, filtered from a yellow solid (A; 1·05 g.), and dried. On distillation the solution gave 3-methyl*cyclo*pent-2-enone (3·8 g.), n_D^{17} 1·4830, b. p. 60—75°/15 mm., and a thick yellow oil (B; 4·0 g.), n_D^{17} 1·6032, b. p. 160—175°/0·3 mm.

The yellow solid (A) α-(*4-keto-2-methyl*cyclo*pent-2-enyl*)*benzyl alcohol* (VIII) separated from ethanol in colourless prisms, m. p. 158° (Found: C, 77·6; H, 7·1; *C*-Me, 6·4. $C_{13}H_{14}O_2$ requires C, 77·2; H, 6·9; 1*C*-Me, 7·4%). Its infra-red absorption spectrum (paraffin paste) showed maxima at 2·97 (OH), 3·26 (very small; possibly associated OH), 5·98 (αβ-unsaturated 5-membered ring ketone), 6·19 (double bond), and at 6·69 mμ (aromatic double bonds).

This alcohol (0·5 g.) was heated under reflux in acetic anhydride (5 c.c.) for 18 hours. [Refluxing in methanol (50 c.c.) containing concentrated sulphuric acid (1 c.c.) for 10 minutes followed by neutralisation by dilute sodium carbonate solution and evaporation of the methanol gave the same result.] After cooling, the solution was decomposed with water, basified, and extracted with chloroform. Evaporation of the dried extract gave 4-benzylidene-3-methyl*cyclo*pent-2-enone (IX) which crystallised from light petroleum (b. p. 60—80°) in colourless prisms, m. p. 122° (Found: C, 84·5; H, 6·3; *C*-Me, 8·0. $C_{13}H_{12}O$ requires C, 84·7; H, 6·5; 1*C*-Me, 8·2%). The 2 : 4-*dinitrophenylhydrazone*, prepared from the alcohol or its dehydration product with 2 : 4-dinitrophenylhydrazine in methanolic sulphuric acid, separated from ethyl acetate in dull red prisms, m. p. 245° (decomp.) (Found: C, 62·5; H, 4·2; N, 15·7. $C_{19}H_{16}O_4N_4$ requires C, 62·6; H, 4·4; N, 15·4%).

The oil, B, on treatment with the 2 : 4-dinitrophenylhydrazine reagent in the cold, gave an immediate deep red precipitate (C); filtration followed by boiling gave a second deep red precipitate (D). The latter separated from ethyl acetate in deep red prisms, m. p. 242° (decomp.), and was identical (mixed m. p. and analysis) with 4-benzylidene-3-methyl*cyclo*pent-2-enone 2 : 4-dinitrophenylhydrazone. The material C crystallised from ethyl acetate in bright red needles, m. p. 274° (decomp.) alone or mixed with 3-styryl*cyclo*pent-2-enone 2 : 4-dinitrophenylhydrazone, described below (Found: C, 62·7; H, 4·7; N, 15·2%).

A second portion (2·1 g.) of B was chromatographed in benzene–light petroleum (b. p. 60—80°) (1 : 1) on alumina (30 g.). Elution with the same solvent (100 c.c.) gave a colourless solid (E; 0·55 g.); little material was eluted with benzene, and the ethyl acetate eluate on evaporation gave a yellow oil (F, 1·3 g.). Material E crystallised from light petroleum (b. p. 60—80°) as needles, being 3-*styryl*cyclo*pent-2-enone*, m. p. 101—102° (Found: C, 84·2; H, 6·3; *C*-Me, 0·0, 0·0. $C_{13}H_{12}O$ requires C, 84·7; H, 6·5%). The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in bright red needles, m. p. 274° (decomp.) (Found: C, 63·1; H, 4·2; N, 15·5. $C_{19}H_{16}O_4N_4$ requires C, 62·6; H, 4·4; H, 15·4%). The oil F was proved to be largely a mixture of the benzyl alcohol and its dehydration product by complete dehydration with boiling acetic anhydride.

The author records his indebtedness to Sir Robert Robinson, F.R.S., for his interest and encouragement, to Dr. F. B. Strauss for the ultra-violet and infra-red measurements, and to the Nuffield Foundation (Oliver Bird Fund) for financial support.

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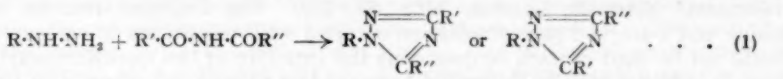
657. *Triazoles. Part I. Unsymmetrical Einhorn–Brunner and Related Pellizzari Reactions.*

By M. R. ATKINSON and J. B. POLYA.

Reactions of phenylhydrazine with *N*-formylbenzamide, *N*-acetylbenzamide, and *N*-acetylpropionamide in the presence of acid catalysts result in the formation of single triazoles, the substituent derived from the stronger acid related to the diacylamine appearing in the 3-position. The new compounds 3-ethyl-5-methyl-1-phenyl- and 3-methyl-1 : 5-diphenyl-1 : 2 : 4-triazole were obtained, the former through the Pellizzari reaction and the latter through both the Pellizzari and the Einhorn–Brunner reaction, in addition to new compounds (not triazoles) of unknown structure.

CONDENSATION of a hydrazine with a diacylamine as in (1) (R, R′, and R″ = H, alkyl, aryl, etc.), to afford substituted 1 : 2 : 4-triazoles, may be termed the Einhorn–Brunner reaction (Einhorn and Szelinsky, *Annalen*, 1905, **343**, 229; Brunner, *Ber.*, 1914, **47**, 2671; *Monatsh.*, 1915, **36**, 509). If R′ and R″ are different, the reaction is said

to be unsymmetrical and could lead to two isomeric triazoles. The only recorded synthesis of this kind is that of 1 : 5-diphenyl-1 : 2 : 4-triazole from phenylhydrazine and



. . . (1)

N-formylbenzamide in aqueous acetic acid (Einhorn and Szelinsky, *loc. cit.*; Thompson, *J. Amer. Chem. Soc.*, 1951, **73**, 5914). A variation of this synthesis, and reactions of *N*-acetylpropionamide and *N*-acetylbenzamide with phenylhydrazine, are summarized in the Table.

Reaction of unsymmetrical diacylamines with equimolar amounts of phenylhydrazine in the presence of acid.

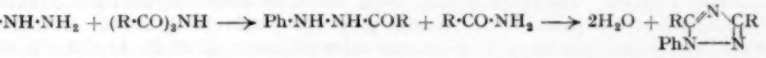
R'·CO·NH·COR''					Substituents in 1 : 2 : 4-triazoles				
R'	R''	Ph·NH·NH$_2$	Solvent	Time (hours)	1	3	5	Yield (%)	By-products and yields (%)
Me	Et	Base	AcOH–NaOAc	16	Ph	Me	Et	45—48	
Me	Et	Hydrochloride	do. +H$_2$O	16	Ph	Me	Et	48	
Me	Et	,,	Pyridine	4	Ph	Me	Et	65	Ph·NH·NHAc 18
Me	Ph	,,	AcOH–NaOAc	10	Ph	Me	Ph	78	
Me	Ph	,,	Pyridine	4	Ph	Me	Ph	35	$C_{23}H_{21}O_4N_5$?
Me	Ph	,,	Pyridine–H$_2$O	5	—	—	—	0	NH_4Cl 36
									Ph·NH·NH·COPh 19
H	Ph	,,	Pyridine	4 [a]	Ph	H	Ph	52	
H	Ph	Base	30% AcOH	1	Ph	H	Ph	84 [b]	

[a] Main yield in few minutes. [b] Thompson, *loc. cit.*

Careful investigation failed to reveal the presence of more than one triazole in any reaction mixture and the same reactants afforded the same triazole irrespective of the composition of the solvent–catalyst system. The reactions investigated up to the present are not ambiguous and the substituent derived from the stronger acid related to the diacylamine appears in the 3-position of the resulting triazole. Further work is in progress to check the validity of these findings in general. A detailed discussion of the mechanism of the Einhorn–Brunner reaction will be presented in another communication but the following principles may be stated at present.

The participation of diacylamines in the reaction as *N*-acylimidic acid, R'·CO·N:C(OH)·R'', or a related structural form, was postulated by Brunner (*loc. cit.*) and made probable by other evidence (Titherley and Stubbs, *J.*, 1914, **105**, 299; Polya and Spotswood, *Rec. Trav. chim.*, 1949, **68**, 573; 1951, **70**, 146). The reaction takes place in the presence of acidic catalysts only (acetic acid, acidic buffers, pyridine hydrochloride), but excessive acid catalysis reduces the yield of triazole and enhances the formation of acylated hydrazines, ammonium chloride, and occasionally compounds of unknown structure.

Brunner examined and dismissed the possibility of a reaction mechanism illustrated by :



This view has been confirmed, and the proof against such a mechanism has been completed, by showing that the second of these reactions does not occur even in the presence of acid catalysts under the mild conditions of the Einhorn–Brunner reaction. Such reactions occur, however, in the absence of solvents at high temperatures and are termed Pellizzari reactions (Pellizzari, *Gazzetta*, 1911, **41**, II, 20, who gives references to previous work). When the acyl groups of the amide and acylhydrazine are different, the Pellizzari reaction may occur with reacylation (interchange of acyl groups), leading to a mixture of triazoles. This is not always the case, and the formation of a single triazole of the correct molecular formula justifies the assumption of an unambiguous reaction and thus determines the structure of the triazole. This is the case with the hitherto undescribed 3-ethyl-5-methyl-1-phenyl-1 : 2 : 4-triazole, which is formed from acetamide and 1-phenyl-2-propionylhydrazine at temperatures not exceeding 210°; 3 : 5-dimethyl-1-phenyl- and 3 : 5-diethyl-1-phenyl-1 : 2 : 4-triazole are not formed although the former appears as a substantial

by-product at higher temperatures. The structure of the new triazole is confirmed by showing it to be different from the unambiguously prepared 5-ethyl-3-methyl-1-phenyl-1 : 2 : 4-triazole (Gastaldi, *Gazzetta*, 1923, **53**, 629). The Pellizzari reaction between benzamide and 1-acetyl-2-phenylhydrazine occurred with reacylation in our experiments and could not be used in itself to determine the structure of the methyldiphenyltriazole obtained in addition to 3 : 5-dimethyl-1-phenyl-1 : 2 : 4-triazole. Since the former is different from the unambiguously prepared 5-methyl-1 : 3-diphenyl-1 : 2 : 4-triazole (Jerchel and Kuhn, *Annalen*, 1950, **568**, 185), it must be the unrecorded 3-methyl-1 : 5-diphenyl-1 : 2 : 4-triazole. When the last-mentioned Pellizzari reaction is carried out at lower temperatures and for shorter times, it is possible to isolate a new substance $C_{15}H_{17}O_2N_3$, apparently an addition compound which is not accompanied by triazoles. Triazoles could not be obtained by replacing amides with nitriles in the Pellizzari reaction. On the contrary, the low yields afforded by most Pellizzari reactions are due to losses through the formation of nitriles which do not participate in the reactions leading to triazoles except in the presence of condensing agents such as sodium (von Walther, *J. pr. Chem.*, 1894, **50**, 91; Engelhardt, *ibid.*, 1896, **54**, 143).

Experimental

M. p.s corrected. The analysis of triazoles, and particularly of triazole picrates, gives consistently low nitrogen values, whereas no difficulty is experienced with the carbon and hydrogen analyses; this is confirmed by a private communication from Dr. F. Lions.

N-Acetylpropionamide and *N*-acetylbenzamide were prepared by Polya and Spotswood's methods (*Rec. Trav. chim.*, 1948, **67**, 927). *N*-Formylbenzamide was prepared by Mr. P. L. Tardrew (Einhorn, Bischkopff, and Szelinsky, *Annalen*, 1905, **343**, 223). 1-Acetyl-2-phenylhydrazine was available as the by-product of the preparation of 3 : 5-dimethyl-1-phenyl-1 : 2 : 4-triazole (Brunner, *loc. cit.*, 1915). Other 1-acyl-2-phenylhydrazines prepared by recorded methods were: formyl (de Vries, *Ber.*, 1894, **27**, 152); propionyl (Leighton, *Amer. Chem. J.*, 1898, **20**, 676); benzoyl (Fischer, *Annalen*, 1878, **190**, 67, 125).

Phenylhydrazine and N-*Acetylpropionamide.*—(*a*) Phenylhydrazine hydrochloride (31·5 g.), *N*-acetylpropionamide (25·0 g.), and dry pyridine (100 c.c.) were refluxed for 4 hours. The product was poured into 5% aqueous sodium hydroxide (250 c.c.) and extracted 3 times with ether, the ethereal extracts being combined with the pyridine layer. Removal of ether and pyridine hydrate left an oil (39·1 g.) which was extracted with ether. Fractionation of the extract gave an oil, b. p. 147—155°/12 mm. (21·5 g.), and 1-acetyl-2-phenylhydrazine, m. p. 128—130° (4 g.), as residue. The oil was redistilled, to afford 5-ethyl-3-methyl-1-phenyl-1 : 2 : 4-triazole, b. p. 122—122·5°/2 mm. (18 g., 65%) (Found: C, 70·8; H, 6·9; N, 21·8. Calc. for $C_{11}H_{13}N_3$: C, 70·6; H, 6·9; N, 22·5%).

(*b*) Freshly crystallized phenylhydrazine hydrochloride (7·3 g.), *N*-acetylpropionamide (7·3 g.), glacial acetic acid (1·5 g.), and hydrated sodium acetate (3·5 g.) were refluxed in water (80 c.c.) for 16 hours at initial and final pH 5. The resulting mixture of aqueous phase and oil was treated with 5% mercuric chloride solution, with stirring at 60°, until no further precipitation occurred. Recrystallization from water afforded the mercuric chloride adduct of 5-ethyl-3-methyl-1-phenyl-1 : 2 : 4-triazole, m. p. 148—152° (14·3 g., 62%); it had m. p. 156° on further recrystallization from 1 : 1 ethanol–ether (Found: C, 29·2; H, 2·9; N, 8·6. Calc. for $C_{11}H_{11}N_3,HgCl_2$: C, 28·8; H, 2·8; N, 9·2%). The adduct was dissolved in cold 4N-hydrochloric acid (100 c.c.) and extracted with ether. The extract was discarded and the acid solution treated with hydrogen sulphide, neutralized to pH 5 with ammonia, and precipitated with sodium carbonate. Ether-extraction of the precipitate and filtrate afforded 5-ethyl-3-methyl-1-phenyl-1 : 2 : 4-triazole, b. p. 281—282/760 mm., d_{20}^{20} 1·075, n_D^{20} 1·5450 (4·5 g., 77% recovery from the adduct, 48% overall); this gave a picrate, yellow rhombs, m. p. 139—140·5°, and a hydrochloride, m. p. 205—206°, which did not depress the m. p.s of those prepared from 5-ethyl-3-methyl-1-phenyl-1 : 2 : 4-triazole obtained by Gastaldi's method (*loc. cit.*).

(*c*) Phenylhydrazine (base), *N*-acetylpropionamide, glacial acetic acid, and anhydrous sodium acetate (each 0·1 mole) were heated on the water-bath for 16 hours and worked up as in (*b*), to afford the same triazole, b. p. 151—155°/9—12 mm. (8·3—8·5 g., 45—48%), as shown by the identity of picrates, hydrochlorides, and mercuric chloride adducts.

2-Phenyl-1-propionylhydrazine and Acetamide.—2-Phenyl-1-propionylhydrazine (3·7 g.) and acetamide (10 g.) were heated at 175° for 9 hours. Much acetonitrile was formed, no triazole

could be isolated, and the hydrazine was recovered in a yield of 96%. 2-Phenyl-1-propionylhydrazine (180 g.) and dry, freshly distilled acetamide (60 g.) were heated at 60° for 14 hours; the temperature was raised slowly to 210° and kept thereat for 6 hours while volatile products distilled off. The residual viscous oil was fractionated, giving acetamide, b. p. 108—109°/15 mm. (33 g.), the triazole, b. p. 152—162°/12 mm. (20 g.), and 2-phenyl-1-propionylhydrazine, b. p. 164°/12 mm., m. p. 158—159° (85 g.). The triazole, refractionated, gave a mixture, b. p. 92—110°/2 mm., of acetamide and triazole (1·5 g.), *3-ethyl-5-methyl-1-phenyl-1 : 2 : 4-triazole* (16 g., 17% on unrecovered 1-propionyl-2-phenylhydrazine or 21% on unrecovered acetamide), b. p. 116—118°/2 mm., and a fraction, b. p. 120—134°/2 mm., contaminated with 2-phenyl-1-propionylhydrazine. The pure triazole (Found: C, 70·7; H, 6·9; N, 21·9. $C_{11}H_{13}N_3$ requires C, 70·6; H, 6·9; N, 22·5%) had b. p. 278°/755 mm., d_{20}^{20} 1·058, n_D^{20} 1·5505. When evaporated with excess of hydrochloric acid and dried *in vacuo* on porous plate over solid potassium hydroxide the triazole affords the hydrochloride, m. p. 208—210°, decomp. 220°. The mercuric chloride adduct crystallizes from 50% ethanol in colourless needles, m. p. 138—140°. The picrate, formed in ethanol solution without warming, consists of yellow, monoclinic prisms, m. p. 138—140°; on further recrystallizations from 1 : 2 chloroform–ethanol and then from 90% ethanol, it had m. p. 141—142°; it depressed the m. p. of picrates of 5-ethyl-3-methyl-1-phenyl-1 : 2 : 4-triazole prepared by the Gastaldi or the Einhorn–Brunner method (7—8° for approximately 1 : 1 mixtures). The different crystal forms of the picrates of the closely similar isomeric triazoles in this case may be used for their rapid identification.

Phenylhydrazine and N-Formylbenzamide.—Phenylhydrazine hydrochloride (14·5 g.) and *N*-formylbenzamide (14·7 g.) in pyridine (50 c.c.) were refluxed for 4 hours although most of the reaction is completed in about 15 minutes, as judged by the volume of oil separating in the reaction. On cooling, prismatic needles of 1 : 5-diphenyl-1 : 2 : 4-triazole, m. p. 89—90°, were obtained (11·5 g., 52%), raised to 90—90·5° after recrystallization from light petroleum (b. p. 60—80°) (Found: C, 76·1; H, 5·1; N, 18·5. Calc. for $C_{14}H_{11}N_3$: C, 76·0; H, 5·0; N, 19·0%). The triazole, its picrate, m. p. 142—143°, and mercuric chloride adduct, m. p. 126—128° (from 80% ethanol), were identical with 1 : 5-diphenyl-1 : 2 : 4-triazole (Young, *J.*, 1895, **67**, 1063) and its derivatives.

1-Formyl-2-phenylhydrazine and Benzamide.—1-Formyl-2-phenylhydrazine (27·2 g.) and benzamide (25 g.) were heated to 220° for 4 hours, volatile products being allowed to distil off during the reaction (4 g.). The mixture was then poured into 10% potassium hydroxide solution (200 c.c.) and extracted with ether (3 × 50 c.c.), the extract evaporated, and the residue fractionated, giving 1-phenyl-1 : 2 : 4-triazole (2·0 g., 7%), b. p. 144—148°/10 mm.; the picrate had m. p. 156—158° alone or mixed with that of the triazole prepared by Pellizzari and Ferro's method (*Gazzetta*, 1898, **28**, II, 541). A second fraction (1·7 g., 4%), b. p. 158—160°/4 mm., m. p. 60—70° (after sublimation, m. p. 85—90°), was 1 : 5-diphenyl-1 : 2 : 4-triazole; neither this nor its picrate (m. p. 136—138°) depressed the m. p. of authentic material (Young, *loc. cit.*).

Phenylhydrazine and N-Acetylbenzamide.—(*a*) Phenylhydrazine hydrochloride (14·5 g.), *N*-acetylbenzamide (16·5 g.), glacial acetic acid (30 c.c.), and anhydrous sodium acetate (10 g.) were refluxed for 10 hours. The product was made alkaline with 40% sodium hydroxide solution and extracted with ether. The pale oil obtained from the extract solidified slowly and consisted of *3-methyl-1 : 5-diphenyl-1 : 2 : 4-triazole*, which formed prisms, m. p. 80—81° on recrystallization from 90% ethanol and then light petroleum (b. p. 60—80°) (18·4 g., 78%) (Found: C, 76·6; H, 5·5; N, 17·6. $C_{15}H_{13}N_3$ requires C, 76·6; H, 5·5; N, 17·9%). The hydrochloride is precipitated when an ethereal solution of the triazole is treated with dry hydrogen chloride; it has m. p. 221—223°; the picrate forms yellow prisms (from ethanol), m. p. 152—154°, and the mercuric chloride adduct needles (from 50% ethanol), m. p. 121—124°. The triazole and its derivatives depress the m. p.s of 5-methyl-1 : 3-diphenyl-1 : 2 : 4-triazole (prepared according to Jerchel and Kuhn, *loc. cit.*) and its derivatives.

(*b*) Phenylhydrazine hydrochloride (14·5 g.) and *N*-acetylbenzamide (16·4 g.) in dry pyridine (50 c.c.) were refluxed for 4 hours. After removal of the pyridine in steam, the oil and the aqueous layer were separated. Cooling the aqueous layer gave an unidentified *substance* as colourless needles, m. p. 103° (1·6 g.) (Found: C, 67·1; H, 6·0; N, 14·3. $C_{28}H_{31}O_4N_5$ requires C, 67·2; H, 6·2; N, 14·0%). Recrystallization of the oil from light petroleum (b. p. 60—80°) afforded more of this material (1·4 g.). From the mother-liquors 3-methyl-1 : 5-diphenyl-1 : 2 : 4-triazole was obtained (7·6 g., 35%), having m. p. 78°, identical with the triazole obtained as in (*a*). Repetition with half the quantities in pyridine containing 5% of water did not afford a triazole but gave the following products (yields calc. on unrecovered *N*-acetylbenzamide): ammonium chloride (0·92 g., 52%); phenylhydrazine hydrochloride (4·1 g., 57%); 1-benzoyl-2-

phenylhydrazine, m. p. 167° (2·1 g., 27%). *N*-Acetylbenzamide was recovered in a yield of 2·5 g. (30%).

1-*Acetyl-2-phenylhydrazine and Benzamide.*—(*a*) 1-Acetyl-2-phenylhydrazine (10 g.) and benzamide (10 g.) were heated in an oil-bath to 185° during 1 hour, then kept at 175—185° for 4 hours and finally at 200° for 1 hour. The residual pale brown oil solidified on cooling. It was dissolved in water (300 c.c.), boiled with Norite, filtered, brought to pH 8 with ammonia, and cooled, affording a mixture of rhombic prisms and needles, m. p. 96—120° (10·6 g.). When dissolved in warm 0·1N-hydrochloric acid and cooled, this afforded benzamide, m. p. 128—129° (4·6 g.). The acid solution was extracted with ether (2 × 50 c.c.), affording 1-acetyl-2-phenylhydrazide, m. p. 128—130° (2·8 g.). The aqueous solution was brought to pH 10 with ammonia and extracted with ether (3 × 100 c.c.) from which colourless prisms, m. p. 105—107°, were obtained (2·3 g., 18% on unrecovered 1-acetyl-2-phenylhydrazine, 19% on unrecovered benzamide) [Found: C, 66·2; H, 6·3; N, 15·5. $C_{15}H_{17}O_2N_3$ (*i.e.*, Ph·NH·NHAc + Ph·CO·NH_2) requires C, 66·4; H, 6·3; N, 15·5%]. The *substance* gave neither picrate nor mercuric chloride adduct; it deteriorated on sublimation or recrystallization from aqueous ethanol.

(*b*) 1-Acetyl-2-phenylhydrazine (11·5 g.) and benzamide (9·1 g.) were heated in an oil-bath at 180° for 4 hours, then at 245° for 4 hours with evolution of ammonia and water. The viscous oil was warmed and poured into 40% aqueous potassium hydroxide (100 c.c.), leaving a little brown oil. The mixture was extracted with ether (3 × 100 c.c.), and the extract was freed from phenylhydrazine and 1-acetyl-2-phenylhydrazine by Brunner's process (Brunner, *loc. cit.*, 1915). Fractionation gave a partly crystallizing forerun (0·8 g.), then 1-acetyl-2-phenylhydrazide, b. p. 158—165°/2—4 mm., m. p. 129—130° (2·9 g.), and 3-methyl-1 : 5-diphenyl-2 : 4-triazole, b. p. 170—195°/2—4 mm., m. p. 79—80° (0·75 g., 5·6% on unrecovered 1-acetyl-2-phenylhydrazine) (Found: C, 76·6; H, 5·5; N, 17·5. Calc. for $C_{15}H_{13}N_3$: C, 76·6; H, 5·5; N, 17·9%). The triazole and its derivatives were identical with 3-methyl-1 : 5-diphenyl-1 : 2 : 4-triazole and its derivatives obtained by the Einhorn–Brunner reaction and distinct from the triazole and derivatives obtained according to Jerchel and Kuhn. The forerun was separated by filtration into crystalline 1-acetyl-2-phenylhydrazine, m. p. 129° (0·1 g.), and an oil identified as 3 : 5-dimethyl-1-phenyl-1 : 2 : 4-triazole (0·6 g.) through the picrate, m. p. 155—157°.

1-*Benzoyl-2-phenylhydrazine and Acetamide.*—(*a*) The reaction between 1-benzoyl-2-phenylhydrazine and acetamide at 140° during 1 hour and then at 175° during 4 hours did not afford triazoles, but 90% of the reactants were recovered.

(*b*) 1-Benzoyl-2-phenylhydrazine (6·0 g.) and dry, freshly distilled acetamide (15 g.) were refluxed in an oil-bath at 250° for 4 hours. The acetamide was distilled off at atmospheric pressure and the residue was extracted with ether (2 × 50 c.c.), leaving undissolved 1-benzoyl-2-phenylhydrazine, m. p. 166° (2·1 g.). The crude triazole extract (3·8 g.) was fractionated to give as main fraction a pale yellow oil, b. p. 210—215°/25 mm., which solidified after several months (2·1 g.). Recrystallization from light petroleum (b. p. 40—60°) removed 1-acetyl-2-phenylhydrazine, m. p. 129° (0·08 g.). The petroleum extract was sublimed at 40°/2 mm., to afford oily crystals, m. p. 80—85°; it gave a *picrate*, flat prisms, m. p. 180—182°, which, recrystallized from ethanol, had m. p. 184—186° (Found: C, 54·6; H, 3·6; N, 17·0. $C_{21}H_{16}O_7N_6$ requires C, 54·3; H, 3·45; N, 18·1%). The substance and its derivative were not identical with the various samples of 3-methyl-1 : 5-diphenyl-1 : 2 : 4-triazole and its picrate but identical with the 5-methyl-1 : 3-diphenyl-1 : 2 : 4-triazole (Jerchel and Kuhn, *loc. cit.*) and its picrate respectively. The triazole from the Pellizzari reaction is somewhat impure since its m. p. is lower than that of the triazole prepared according to Jerchel and Kuhn.

(*c*) 1-Benzoyl-2-phenylhydrazine (95 g.) and acetamide (50 g.) were heated at 260—280° for 3 hours, water and other volatile substances being allowed to distil off (40 g.). The residue was poured into 10% aqueous sodium hydroxide (250 c.c.), and the resulting mixture was extracted with ether (3 × 50 c.c.). The oil (85 g.) from the extract was fractionated, giving a forerun 110—120°/14 mm. (6·1 g.), 3 : 5-dimethyl-1-phenyl-1 : 2 : 4-triazole, b. p. 134—138°/3 mm., 118—124/2 mm. (27·6 g., 70% on unrecovered 1-benzoyl-2-phenylhydrazine) (picrate, m. p. 154—156°; mercuric chloride adduct, m. p. 186—189°), and 1-benzoyl-2-phenylhydrazine, b. p. 172—180°/2 mm., m. p. 167—168° (47 g.).

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658. *Perfluoroalkyl Grignard Reagents. Part I. The Preparation and Some Reactions of Heptafluoro-n-propylmagnesium Iodide.*

By R. N. Haszeldine.

The factors influencing the formation of heptafluoro-*n*-propylmagnesium iodide have been examined, and experimental directions are given for the preparation of this reagent in yields of 80% at low temperature, with high dilution in donor solvents, by using pure magnesium. Decomposition of the Grignard reagent yields heptafluoropropane, hexafluoropropene, traces of perfluoro-*n*-hexane and a hexafluoropropene polymer, and the mechanism of formation of these compounds is discussed; by-products from the solvent have been identified. The concept of loss of fluorine as fluoride from a fluoro-anion is discussed. The carbonation of heptafluoropropylmagnesium iodide gives heptafluorobutyric acid in yields of 75—80%. Formaldehyde, acetaldehyde, and acetone react with the Grignard reagent to give the expected primary, secondary, and tertiary alcohols, respectively.

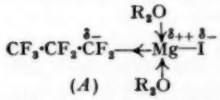
This series of communications describes the preparation and reactions of perfluoroalkyl and perfluoro*cyclo*alkyl Grignard reagents, derived from perfluoro-organic bromides and iodides. Summaries of the results have been given (*J.*, 1950, 2789; *Nature*, 1951, **167**, 139; **168**, 1028; 120th Meeting, Amer. Chem. Soc., September, 1951).

The preparation of Grignard reagents from fluorine compounds has been achieved only with compounds containing fluorine, hydrogen, and another halogen (McBee and Truchan, *J. Amer. Chem. Soc.*, 1948, **70**, 2910; Haszeldine, *J.*, 1951, 588, 2459, and unpublished), and attempts to prepare Grignard reagents from hydrogen-free polyhalogeno-compounds [*e.g.*, bromotrichloromethane and trichloroiodomethane (Simons, Sloat, and Meunier, *J. Amer. Chem. Soc.*, 1939, **61**, 435)] have hitherto been unsuccessful. Brice, Pearlson, and Simons (*ibid.*, 1946, **68**, 968) observed that a bromoheptafluoropropane reacted with magnesium in the presence of ether, and visualised the product as a Grignard reagent, since addition of water yielded a heptafluoropropane. This observation alone does not necessarily indicate Grignard formation, since it has been found that bromofluoro-compounds can be reduced to the hydrofluoro-compounds under similar conditions.

The conditions which have been found to affect the formation and reactions of perfluoroalkyl Grignard reagents are: (i) the magnesium used, (ii) the initiation of the reaction, (iii) the solvent, (iv) the dilution of the fluoro-iodide in the solvent, (v) the temperature, and (vi) the conditions for the reaction of the Grignard reagent with the second component. The main cause of instability in the transient Grignard reagents obtained in earlier experiments (Emeléus and Haszeldine, *J.*, 1949, 2953) has been traced to conditions (i) and (vi).

Perfluoroalkyl Grignard reagents are apparently much more sensitive to traces of impurities in the magnesium than are their hydrocarbon analogues, but smooth Grignard formation occurs when spectroscopically pure magnesium, or magnesium substantially free from traces of metals such as cobalt, iron, nickel, or manganese, is used. Suitable methods for the preparation of the magnesium and for the initiation of the reaction are described in the Experimental.

The solvent plays an important part in the formation of Grignard compounds. Little or no Grignard compound can be obtained from heptafluoroiodopropane and magnesium in perfluoromethyl*cyclo*hexane, diperfluoro-*n*-butyl ether, or benzene, and at higher temperatures the main products are magnesium iodide and fluoride, hexafluoropropene, and (in benzene) heptafluoropropane. These reaction media are poor solvents for the Grignard reagent and for magnesium iodide or fluoride formed on the surface of the magnesium, and thus tend to promote coating effects. Since the C–Mg bond in heptafluoropropyl-magnesium iodide will be more ionic than in, say, propylmagnesium iodide, good donor solvents facilitate its formation and stabilisation, by formation of complexes, such as (*A*). Ethyl and *n*-butyl ether have therefore been used for much of



(*A*)

the work now recorded, but improved results can be obtained with tetrahydropyran and with *tert.*-amines; not only is the Grignard reagent produced in higher yield, but it is stable to a much higher temperature.

The use of concentrated solutions of the fluoroiodide causes appreciable side-reactions with the formation of heptafluoropropane, polymeric material, and products arising from the solvent. Thus, when acetaldehyde-free ethyl ether is used as solvent under such conditions, the pentanol (I), ethane, ethylene, and acetaldehyde are formed; decomposition of the Grignard reagent into a heptafluoropropyl radical is postulated to account for these products:

$$C_3F_7\cdot + C_2H_5\cdot O\cdot C_2H_5 \longrightarrow CH_3\cdot\dot{C}H\cdot O\cdot CH_2\cdot CH_3 + C_3F_7H$$

$$CH_3\cdot\dot{C}H\cdot O\cdot CH_2\cdot CH_3 \longrightarrow C_2H_5\cdot + CH_3\cdot CHO$$

$$\downarrow \qquad \downarrow C_3F_7MgI$$

$$C_2H_4 + C_2H_6 \quad C_3F_7\cdot CH(OH)\cdot CH_3 \qquad (I)$$

The Grignard reagent is much more stable in dilute solution.

One of the main differences between fluoroalkyl and normal Grignard reagents is the temperature-instability of the former, *i.e.*, they must be prepared and used at abnormally low temperatures (−50° to 0°); above 20° decomposition of the heptafluoropropylmagnesium iodide, mainly to heptafluoropropane, is rapid. Because of this instability during formation and storage, it has often been found convenient to have the second component (*e.g.*, carbon dioxide or a carbonyl compound) present throughout the reaction, so that it can combine with the organometallic derivative as soon as the latter is formed. Carbon dioxide reacts with heptafluoropropylmagnesium iodide to give heptafluorobutyric acid (thereby proving that a Grignard compound has been formed) at temperatures down to −80°, and this reaction provides a simple alternative to the oxidation route described earlier (Haszeldine, *J.*, 1950, 2789; *Nature*, 1950, **166**, 192) for the conversion of fluoroiodides into fluoro-acids.

The by-products from the interaction of magnesium and heptafluoroiodopropane in a solvent are heptafluoropropane, hexafluoropropene, traces of perfluoro-*n*-hexane, by-products from the solvent, a brown resinous polymer, and magnesium iodide and fluoride. It is suggested that the decomposition of the Grignard reagent during its formation or storage yields hexafluoropropene *via* the heptafluoropropyl anion:

$$CF_3\cdot CF_2\cdot CF_2\cdot MgI \longrightarrow CF_3\cdot CF_2\cdot CF_2^- + \overset{+}{M}gI \qquad CF_3{-}\overset{F}{CF}{-}CF_2^- \longrightarrow CF_3{-}CF{=}CF_2 + F^-$$

Decomposition of heptafluoropropylmagnesium iodide to a heptafluoropropyl *radical* would undoubtedly be followed by hydrogen-abstraction from the solvent to give heptafluoropropane (cf. Banus, Emeléus, and Haszeldine, *J.*, 1950, 3041); furthermore, the formation of hexafluoropropene from this radical by disproportionation would involve homolytic C–F fission and is therefore unlikely. The known reactivity of the heptafluoropropyl radical also excludes radical combination as the mechanism for the formation of perfluoro-*n*-hexane, so that the bimolecular reaction, $C_3F_7\cdot MgI + C_3F_7I \longrightarrow C_6F_{14} + MgI_2$, is presumably involved.

The polymer produced during Grignard formation yields hexafluoropropene on pyrolysis and is apparently derived from this olefin by anionic polymerisation:

$$C_3F_7\cdot MgI \longrightarrow C_3F_7^- + \overset{+}{M}gI \qquad C_3F_7^- + C_3F_6 \longrightarrow (CF_3\cdot CF\cdot CF_2\cdot C_3F_7)^-\,(MgI)^+ \xrightarrow{C_3F_6} \text{etc.}$$

The ready addition of alkoxide ion to hexafluoropropene indicates its susceptibility to anionic attack.

The mechanism proposed above for fluoride elimination from a fluoro-anion can be applied to the results obtained by Gilman and Jones (*J. Amer. Chem. Soc.*, 1943, **65**, 2037) and Henne (*ibid.*, 1938, **60**, 2275), that 1 : 1 : 1-trifluoro- and 1 : 1-difluoro-2-iodoethane underwent a ready reaction with magnesium in ether to give 1 : 1-difluoroethylene and vinyl fluoride, respectively, and equimolar amounts of magnesium iodide and fluoride.

These workers considered that the Grignard reagent had not been formed, but it now seems probable that Grignard formation had been effected but under unsuitable conditions, leading to decomposition :

$$CF_3{\cdot}CH_2I \longrightarrow CF_3{\cdot}CH_2{\cdot}MgI \longrightarrow CF_3{\cdot}CH_2^- + \tilde{M}gI$$

$$F\overset{\curvearrowleft}{-}CF_2\overset{\swarrow}{-}CH_2^- \longrightarrow CF_2{=}CH_2 + F^-$$

and similarly

$$CHF_2{\cdot}CH_2{\cdot}MgI \longrightarrow F\overset{\curvearrowleft}{-}CHF\overset{\swarrow}{-}CH_2^- \longrightarrow CHF{=}CH_2 + F^-$$

Application of the technique used for the perfluoroalkyl iodides has shown (*Nature*, 1951, **168**, 1028) that 1 : 1 : 1-trifluoro-2-iodoethane yields a Grignard reagent which is stable only at low temperatures and yields 1 : 1-difluoroethylene and small amounts of 1 : 1 : 1-trifluoroethane on decomposition. As might be expected on this basis, 3 : 3 : 3-trifluoropropylmagnesium iodide is perfectly stable at room temperature. The ready formation of perfluoro-olefins on heating the sodium salts of perfluoro-acids (*Nature, loc. cit.*) may also be due to similar fluoro-anion decomposition.

The reaction of the perfluoroalkyl Grignard reagents with carbonyl compounds proceeds normally. Thus heptafluoropropylmagnesium iodide reacts with formaldehyde, acetaldehyde, and acetone to give the expected alcohols, heptafluorobutanol, heptafluoropentan-2-ol, and heptafluoro-2-methylpentan-2-ol in satisfactory yield. More heptafluoropropane is formed by reduction than during the reaction with carbon dioxide under comparable conditions. It is clear, however, that with suitable development in experimental technique, the perfluoroalkyl Grignard reagents will prove of great value in synthetical fluorine chemistry.

Experimental

Heptafluoroiodopropane was used for the present study since its behvaiour is typical of fluoroiodides other than trifluoroiodomethane and pentafluoroiodoethane, and its boiling point enables conventional apparatus to be used. It was prepared by the method described in *J.*, 1949, 2856, and later by extension of the method of *J.*, 1951, 584, to heptafluorobutyric acid. The fluoroiodide (b. p. 39·5°, n_D^{17} 1·329, absorption spectrum in ethanol : $\lambda_{max.}$ 251 mμ ; ε 230) was stored in a vacuum system. Sealed Pyrex 50—500 ml. tubes were used for the early experiments, the reactants and products being transferred *in vacuo*. Conventional Grignard apparatus was also used. Stringent precautions were taken to use anhydrous reactants and exclude moisture, oxygen, and carbon dioxide.

Conditions affecting Formation of Grignard Compounds.—The yield of Grignard reagent in the experiments outlined below (taken from over 300 carried out to determine optimum conditions) was determined (after removal of excess of magnesium, used in all experiments) (*a*) by hydrolysis with water, 5N-hydrochloric acid, or saturated ammonium chloride, or (*b*) by the carboxylation with carbon dioxide as solid or gas, or addition of the Grignard solution to a mixture of solid carbon dioxide and the solvent. Control experiments showed that the hydrolysis and carbonation techniques gave substantially the same result. Heptafluorobutyric acid was isolated as its sodium salt and converted into the amide (*J.*, 1950, 2789) for estimation ; a correction of 10—20%, determined from blank experiments, was applied to cover handling losses. In an alternative procedure the acid was estimated by conversion into silver heptafluorobutyrate.

(a) *Magnesium.* Spectroscopic examination of the magnesium used initially (Emeléus and Haszeldine, *loc. cit.*), which gave yields of *ca.* 70% of Grignard reagents from ethyl iodide or iodobenzene but only about 3% from heptafluoroiodopropane, revealed contamination by traces of cobalt and other metals. Spectroscopically pure magnesium has therefore been used for the results described below. 45—55% Yields of heptafluoropropylmagnesium iodide were obtained (in ethyl or *n*-butyl ether at −30° to 0°) by using magnesium shavings freshly cut from a magnesium rod, but better yields (55—60%, under comparable conditions) resulted if the magnesium rod was cut into fine shavings under anhydrous ether, with oxygen and air excluded. Care was taken to avoid contamination of the magnesium by grease, etc.

(b) *Initiation of reaction.* With magnesium, substantially free from oxide film, formation of Grignard compound was spontaneous ; in other cases a crystal of iodine was added. For formation of Grignard compounds at low temperatures, and with greater conversion of the fluoroiodide, freshly powdered iodine (*ca.* 10% of the amount required to give magnesium

iodide) was heated to 150° with the magnesium in absence of solvent. In an alternative procedure, a 15% excess of magnesium over that required for perfluoroalkyl Grignard formation was added to ether in a flask with a tap at the base. Methyl, ethyl, or phenyl bromide or iodide was added and formation of Grignard compound allowed until 10—15% of the magnesium had dissolved. The Grignard solution was drained off and the washed residual pitted magnesium used immediately for reaction with heptafluoroiodopropane. For experiments at temperatures below −50°, reaction was initiated at −10° to −20° and the temperature was then reduced to that required.

(c) *Solvents.* (i) A series of experiments, with perfluoromethyl*cyclo*hexane (10 ml.) as solvent, between heptafluoroiodopropane (2·0 g.) and magnesium (1·0 g.) in sealed tubes showed that little reaction occurred below 100°, above which increasing amounts of hexafluoropropene and magnesium iodide and fluoride were formed. The yield of olefin at 210° was 10%. Diperfluoro-*n*-butyl ether gave substantially the same results as fluorocarbons, and heptafluorobutyric acid could not be detected after prolonged reaction at 20° in an atmosphere of carbon dioxide. A 5% yield of the acid was obtained after reaction at 35° for 72 hours in benzene in a carbon dioxide atmosphere; at 150°, 60% of the fluoroiodide was recovered and hexafluoropropene (5%) and heptafluoropropane (10%) were isolated.

(ii) The results of typical experiments, in which alkyl ethers, tetrahydropyran, and alkylamines were used as solvents, are given in Table 1. The yields, obtained in experiments with heptafluoroiodopropane (5·0 g.) and magnesium (2·5 g.) in solvent (150 ml.) for 36 hours (carbon dioxide being always present), are based on the quantity of fluoroiodide taken and are the mean of two or three on this scale, the products being combined.

Separation of heptafluoroiodopropane from ethyl ether is difficult, and the fluoroiodide was often converted into heptafluoropropane by heating the ethereal concentrate with alcoholic potassium hydroxide.

TABLE 1. *Yield, %, of Grignard compound (and recovery, %, of starting material) at various temperatures.*

	−60°	−30°	0°	20°	40°			
Et_2O	58(8)	68(5)	59	50(~1)	33			
Bu_2O	62(11)	66(7)	61(8)	49(4)	27(0)			
$[CH_2]_5{>}O$	64(13)	72(7)	65(4)	57(~1)	48(0)			
	−60°	−40°	−20°	−10°	−5°	10°	20°	40°
NMe_3	—	41(13)	56(4)	—	51(6)	—	—	—
NEt_3	27(37)	45(21)	—	52(12)	—	55(2)	56(0)	52(0)

(d) *Dilution.* The effect of dilution is shown in Table 2 for butyl ether at 0°; similar data were obtained for experiments in ethyl ether.

TABLE 2.

Solvent, ml.	5	20	50	100	150
C_3F_7I recovered, %	17	11	12	10	13
By-products, % (C_3F_6, C_3F_7H, and C_6F_{14})	32	18	14	14	16
$C_3F_7{\cdot}MgI$ formed, %	6	15	32	43	59
Decomp., %, in 24 hrs. at −30°	60	31	—	12	14
,, ,, 72 hrs. at −30°	90	74	—	28	26

The marked effect of dilution on the stability of the Grignard reagent is also shown in the Table. Two parallel preparations of the Grignard reagent were made at −30° for each dilution, and the amount of residual Grignard reagent after the storage of one of them for the time shown was measured.

(e) *Temperature.* The data in Table 3, obtained by using magnesium (2·0 g.) and heptafluoroiodopropane (5.0 g.) in ether (150 ml.) for 24 hours (carbon dioxide being present throughout), show the effect of temperature. Similar results were obtained with butyl ether, tetrahydropyran, trimethylamine, and triethylamine.

TABLE 3.

Temp., ° c.	−80	−60	−40	−20	0	10	20	40
C_3F_7I recovered, %	23	9	10	12	7	9	3	0
C_3F_7MgI formed, %	37	55	59	64	58	44	41	27

Heptafluoropropylmagnesium iodide decomposes at a much slower rate at low temperatures : thus, in ethyl ether, the decomposition at −60°, −40°, −20°, 0°, 20°, and 40° after 24, 168, 168,

72, 72, and 36 hours was 2, 29, 38, 48, 75, and 61%, respectively. The decomposition at −40°, 0°, 20°, and 40° after 168, 72, 72, and 40 hours in tetrahydropyran as solvent was 29, 37, 44, and 39%, respectively, showing the increased thermal stability in this solvent.

(f) *Reaction with the second component.* The increase in yield obtained by having the compound for further reaction with the Grignard reagent (*e.g.*, carbon dioxide) present during Grignard formation is illustrated by the following: at −40°, −20°, 0°, and 20° the yields of heptafluorobutyric acid under a particular set of conditions, with carbon dioxide present during Grignard formation, were 57, 65, 56, and 43%, whereas in parallel experiments with carbon dioxide added after the Grignard reagent had been formed the yields were 50, 59, 46 and 23%, respectively.

By-products arising during Formation of Grignard Compounds.—The volatile by-products were 1 : 1 : 1 : 2 : 2 : 3 : 3-*heptafluoropropane* (Found: C, 21·2; H, 0·8%; *M*, 170. C_3HF_7 requires C, 21·2; H, 0·6%; *M*, 170), b. p. −14° (Brice, Pearlson, and Simons, *loc. cit.*, report b. p. −20° for 1 : 1 : 1 : 2 : 3 : 3 : 3-heptafluoropropane), and hexafluoropropene (Found: *M*, 150. Calc. for C_3F_6: *M*, 150), b. p. −28·5° (Henne and Waalkes, *J. Amer. Chem. Soc.*, 1946, **68**, 496, report b. p. −29°). These products were separated by treatment with a slight excess of bromine with exposure to ultra-violet light in a silica tube for 30 minutes, followed by distillation of the 1 : 2-dibromohexafluoropropane (Found: C, 11·5%; *M*, 308. Calc. for $C_3Br_2F_6$: C, 11·6%; *M*, 310), b. p. 71°, n_D^{20} 1·358. *Perfluoro-n-hexane* (Found: C, 21·3%; *M*, 337. C_6F_{14} requires C, 21·3%; *M*, 338), b. p. 56°, was isolated by distillation. Simons ("Fluorine Chemistry," Academic Press, 1950, p. 411) reports b. p. 55·1—56·1° for a perfluorohexane of unknown structure.

The amount of heptafluoropropane as by-product increased from 9% for reaction at −30° to 28% at 40°, while the amounts of hexafluoropropene and perfluorohexane formed were approximately constant at 5% and 2%, respectively. The remaining 15—20% of the product was magnesium iodide and fluoride, resinous polymer, and unidentified materials. The resin (*ca.* 5%) was washed with acid, base, alcohol, and ether, and then heated in a high vacuum. The white sublimate [Found: C, 24·0; H, 0; F, 75·7. Calc. for $(C_3F_6)_n$: C, 24·0; H, 0; F, 76·0%] (*ca.* 10% of the resin) had a similar appearance to a tetrafluoroethylene polymer, but gave hexafluoropropene on pyrolysis. The residue from the sublimation was heated in platinum at 700° in a high vacuum to give a 10% yield of hexafluoropropene, identified as the dibromide; other fluorine-containing pyrolysis products could not be identified on the scale used.

Side-reactions of the Grignard reagent with the solvent gave ethylene and ethane (1—4% yield when Grignard decomposition was at a maximum); experiments in ethyl ether gave 3 : 3 : 4 : 4 : 5 : 5 : 5-*heptafluoropentan-2-ol* (0·4%) (Found: C, 28·3; H, 2·6. $C_5H_5OF_7$ requires C, 28·0; H, 2·3%), b. p. 100—102°, n_D^{20} 1·315, shown to be identical with a specimen prepared as below.

Thermal Decomposition of Heptafluoropropylmagnesium Iodide.—A solution of the Grignard reagent was prepared at −20° in butyl ether (60% yield) and was freed from excess of magnesium and volatile by-products. The solution was then heated rapidly to reflux: there were obtained 76% of heptafluoropropane, 6% of hexafluoropropene, and the remainder was a resin and products involving the solvent.

Optimum Conditions for the Conversion of Heptafluoroiodopropane into Heptafluorobutyric Acid.—From the experiments summarised above, the optimum conditions for Grignard formation and its reaction with carbon dioxide are as follows. To spectroscopically pure magnesium shavings (10 g.; prepared under *n*-butyl ether, freed from dissolved oxygen) and *n*-butyl ether (600 ml.) were added two crystals of iodine. The mixture was stirred and cooled to −10°, a slow stream of carbon dioxide was passed into the flask, and a solution (5 ml.) of heptafluoroiodopropane (30·0 g.) in butyl ether (100 ml.) was added. The solution became cloudy after 5 minutes, and after 20 minutes it was a pale brown. The temperature was then lowered to −30°, and the rest of the fluoroiodide added during 2 hours, small pieces of solid carbon dioxide being added to the reaction mixture, which slowly became brown. Addition of carbon dioxide was continued for 8 hours and stirring for a further 20 hours, during which the temperature was allowed to rise to that of the room. The volatile products in the liquid-air traps were washed with sodium hydroxide solution, dried (P_2O_5), and fractionated *in vacuo* to give heptafluoropropane (7%) and hexafluoropropene (2%). The ethereal solution was decanted from the excess of magnesium and poured slowly into excess of 5N-hydrochloric acid. The ether layer was extracted with sodium hydroxide solution, and the aqueous layer was filtered and extracted with ethyl ether, and the ethereal extract concentrated in presence of 5N-sodium hydroxide. The combined aqueous alkaline extracts were neutralised (bromothymol-blue) and evaporated to dryness *in*

vacuo. The sodium heptafluorobutyrate was extracted by methanol and converted into heptafluorobutyric acid (77%), b. p. 120·5—121°, n_D^{19} 1·297, identified by comparison with a genuine specimen prepared earlier (*J.*, 1950, 2789). After the above alkaline extraction, the butyl ether solution was washed with water, dried, and distilled to give heptafluoroiodopropane (5%) and perfluorohexane (0·5%). The resinous material obtained by filtration was freed from magnesium fluoride by treatment with concentrated acid. The combined inorganic fluoride residues were converted into fluorosilicic acid (F^- equivalent to *ca.* 3% of the heptafluoroiodopropane taken). The total weight balance was thus *ca.* 94%.

Reaction of Heptafluoropropylmagnesium Iodide with Formaldehyde, Acetaldehyde, and Acetone.—Formaldehyde (from trioxymethylene), acetaldehyde (from paraldehyde), and acetone were purified and thoroughly dried in a vacuum system. Heptafluoropropylmagnesium iodide was prepared from heptafluoroiodopropane (10·0 g.) and magnesium (3·2 g.) at −25° in *n*-butyl ether (150 ml.) during 8 hours, and into it was passed an excess of formaldehyde (2·0 g.) during 3 hours. After the mixture had been stirred for a further 8 hours, the temperature was allowed to rise overnight to that of the room, and the reaction mixture was then heated to 60° and the volatile by-products were removed. The reaction mixture was hydrolysed by pouring it on excess of acid, and the ethereal layer was separated, dried (P_2O_5), and distilled to give crude heptafluorobutanol, b. p. 95—105°, which, after being heated with phosphoric oxide at 80° for 3 hours, was redistilled to give 2 : 2 : 3 : 3 : 4 : 4 : 4-*heptafluorobutan*-1-*ol* (42%) (Found: C, 23·9; H, 1·3. $C_4H_3F_7O$ requires C, 24·0; H, 1·5%), b. p. 96·5°, n_D^{10} 1·299. Heptafluoropropane (17%), hexafluoropropene (4%), and unchanged heptafluoroiodopropane (24%) were also isolated.

In similar manner, acetaldehyde (3·0 g.) reacted with heptafluoropropylmagnesium iodide, to give heptafluoropropane (21%), hexafluoropropene (2%), unchanged heptafluoroiodopropane (8%), and 3 : 3 : 4 : 4 : 5 : 5 : 5-heptafluoropentan-2-ol (37%) (Found: C, 27·9; H, 2·1. Calc. for $C_5H_5OF_7$: C, 28·0; H, 2·3%), b. p. 101°. identical with that described above.

Acetone (4 ml.) was added dropwise to a Grignard solution prepared as above (58% yield of heptafluoropropylmagnesium iodide estimated from a parallel carbonation experiment), and gave a 32% yield of 3 : 3 : 4 : 4 : 5 : 5 : 5-*heptafluoro*-2-*methylpentan*-2-*ol* (Found: C, 31·8; H, 3·2. $C_6H_7OF_7$ requires C, 31·6; H, 3·1%), b. p. 106·5—107°, n_D^{25} 1·324. Heptafluoropropane (20%) and unchanged heptafluoroiodopropane (21%) were also isolated.

The yields of the alcohols, when formaldehyde, acetaldehyde, or acetone was added at intervals during Grignard formation under the above conditions, were 49%, 44% and 37%, respectively.

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659. iso*Oxazolones. Part III.** *Some Reactions of Arylaminomethylene*iso*oxazolidones with Bases.*

By G. SHAW.

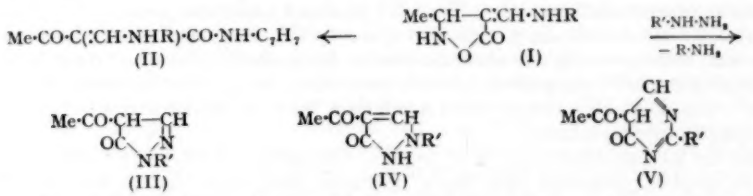
The reaction of arylaminomethylene*iso*oxazolidones (I) with a number of basic substances has been examined. Reaction with *p*-toluidine gave the *p*-toluidide (II); with hydrazines the pyrazolone ketones (III) or (IV); and with aromatic amidines the pyrimidone ketones (V). However, with aliphatic amidines, or more generally with strong bases, a novel rearrangement occurred with formation of the *iso*oxazolidone ketones (VI), and the mechanism of this reaction is discussed. Reaction of either (I; R = *p*-tolyl) or (VI; R = *p*-tolyl) with hydroxylamine was more complex; in each case the same products, namely, *p*-toluidine, the *iso*oxazolone (XI; R″ = *p*-tolyl), and a base $C_{11}H_{14}ON_2$, postulated as a dihydro-1 : 2 : 6-oxadiazine (XII; R = Me, R′ = H, R″ = *p*-tolyl), were isolated.

THE preparation and properties of arylaminomethylene*iso*oxazolidones (I) were described in Parts I and II (*J.*, 1950, 720; 1951, 1017). The present paper is concerned with further reactions of these substances with bases.

* Part II, *J.*, 1951, 1017.

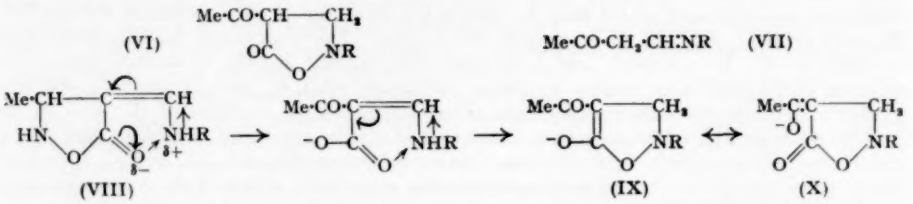
The *iso*oxazolidone (I; R = *p*-tolyl) and *p*-toluidine in hot alcohol gave smoothly the *p*-toluidide (II). This suggested that the *iso*oxazolidones might be used for the synthesis of a variety of heterocyclic systems. Accordingly (I; R = Ph) was treated in boiling ethanol for a short time with hydrazine; ammonia was evolved and an excellent yield of a substance was obtained which may be designated as either of the tautomeric forms (III; R = H) or (IV; R = H) of a pyrazolonyl ketone. The compound, also isolated after reaction of (I; R = *p*-tolyl) and hydrazine, was readily soluble in sodium hydroxide solution and insoluble in sodium hydrogen carbonate solution, and an alcoholic solution gave a reddish-purple colour with ferric chloride. Similarly, reaction of (I; R = Ph or *p*-tolyl) with phenylhydrazine gave a compound of similar solubility behaviour and giving a red colour with alcoholic ferric chloride; this may be formulated as (III or IV; R = Ph). An attempt to oxidise it with sodium hypoiodite solution to either of the known phenylpyrazolones failed.

Analogous reactions occurred rapidly when (I; R = Ph or *p*-tolyl) was heated in boiling ethanol for a short time with benzamidine or *p*-methanesulphonylbenzamidine, giving good yields of the alkali-soluble 2-arylpyrimidones (V; R′ = Ph and *p*-Me·SO_2Ph), the latter being isolated initially as the amidinium salt.



When, however, (I; R = Ph) was heated under reflux in ethanol with aliphatic amidines, including acetamidine, guanidine, and *S*-methyl*iso*thiourea, a smooth reaction occurred with liberation of ammonia but, instead of the expected pyrimidone, a crystalline solid $C_{11}H_{11}O_3N$ was obtained. An analogous substance $C_{12}H_{13}O_3N$ was formed from (I; R = *p*-tolyl) and the amidines. The same compounds were more conveniently prepared by treatment of the *iso*oxazolidones (I; R = Ph and *p*-tolyl) with aqueous or alcoholic sodium hydroxide at room temperature for a few minutes. No reaction occurred, however, with a weak base, *e.g.*, ammonia. The molecular formulæ of these compounds suggested that the arylaminomethylene group had been unaffected during the reaction and this was confirmed by careful alkaline hydrolysis of the substance $C_{12}H_{13}O_3N$ to the ketoanil (VII; R = *p*-tolyl), which on more vigorous hydrolysis gave *p*-toluidine and acetone (cf. Part II, *loc. cit.*). In addition, the compounds were readily soluble in aqueous sodium hydroxide but insoluble in sodium hydrogen carbonate solution, and alcoholic solutions gave red-purple colours with ferric chloride. Thus the compounds may be acetyl*iso*oxazolidones (VI; R = Ph and *p*-tolyl). The mechanism of this novel base-catalysed rearrangement may be as shown below and requires an explanation of the greater reactivity of the *iso*oxazolidones than of analogous *iso*oxazolones (cf. Part II, *loc. cit.*). The activity of the 5-carbonyl group in the *iso*oxazolone ring will be reduced considerably by migrations of the type $-C\overset{\curvearrowright}{=}N\cdot O\cdot C\overset{\curvearrowright}{=}O$ in contrast to the greater activity of analogous oxazolones in which migrations $C\overset{\curvearrowright}{=}N$ increase the positive charge on $C_{(5)}$, *i.e.*, $N\overset{\curvearrowleft}{=}C\cdot O\cdot C\overset{\curvearrowright}{=}O$. In the *iso*oxazolidone system the inhibiting effect of $C\overset{\curvearrowright}{=}N$ is lost, and indeed a small activating effect may be present $CH\cdot\overset{\longleftarrow}{NH}\cdot O\cdot C\overset{\curvearrowright}{=}O$; this results in basicity of the cyclic NH as shown by ready formation of stable hydrochlorides and picrates (cf. Parts I and II, *locc. cit.*). The *iso*oxazolidone system will, however, be stabilised by an exocyclic double bond $NH\cdot O\cdot(C\overset{\curvearrowright}{=}O)\cdot\overset{\curvearrowleft}{C}=C$. In the arylaminomethylene*iso*oxazolidones the movements will be as depicted (VIII), with a slightly positive exocyclic nitrogen atom. Rupture of the ring

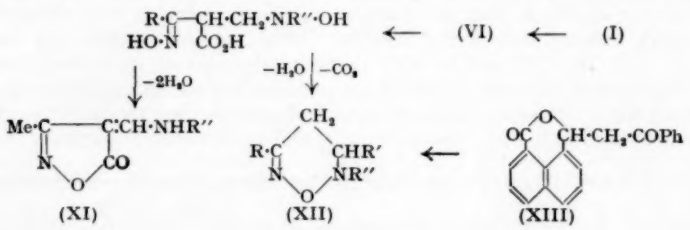
in the presence of a strong base is followed by a prototropic change and formation of the anionic forms (IX and X) of the *iso*oxazolidone ketones, which will be stabilised by movements such as Me·C(O⁻)=C and R·N·O·C=O.



An attempt was made to follow the course of the reaction by titration of the ammonia (or titratable base) formed, the reaction being stopped by addition of excess of acid (a preliminary experiment revealed that the arylaminomethylene*iso*oxazolidone was not sufficiently strong a base to interfere in the titration if methyl-red was used as an indicator). The reaction proceeded too rapidly, however, for an accurate estimation, being substantially complete in aqueous sodium hydroxide at 25° in about 5 minutes.

In an attempt to obtain a thio-analogue of (VI), the reaction of (I; R = *p*-tolyl) with sodium hydrogen sulphide was examined. In alcoholic solution at room temperature, no reaction occurred during several hours, but, when the solution was heated, a vigorous reaction commenced with formation of much dark tar from which only the keto-anil (VII; R = *p*-tolyl) could be isolated.

When the *iso*oxazolidone (I; R = *p*-tolyl) was warmed with 1 equivalent of hydroxylamine in alcohol, ammonia was freely liberated, and from the reaction mixture were isolated *p*-toluidine, 3-methyl-4-*p*-toluidinomethylene*iso*oxazol-5-one (XI; R″ = *p*-tolyl), and a base $C_{11}H_{14}ON_2$. The first product of the reaction appears to be (VI; R = *p*-tolyl) since this gave the same mixture when warmed with hydroxylamine solution. The above-mentioned base, which was colourless, gave a yellow salt with hydrogen chloride: its molecular formula suggests that it may be the dihydro-1 : 2 : 6-oxadiazine (XII; R = Me, R′ = H, R″ = *p*-tolyl) and the mode of formation of such a substance and of (XI) may be as indicated. The only analogous substance recorded is the compound (XII; R = Ph, R′ = 8-carboxy-1-naphthyl, R″ = H) prepared by the reaction of (XIII) and hydroxylamine (Zink, *Monatsh.*, 1901, **22**, 822), a reaction not unlike that between (VI; R = *p*-tolyl) and hydroxylamine. Zink (*loc. cit.*) states that his product gave a yellow colour with hydrochloric acid. The formation of *p*-toluidine is not indicated in the scheme but would occur by the reaction >C:CH·NHR + NH_2·OH ⟶ >C:CH·NH·OH + RNH_2.



Experimental

α-p-*Toluidinomethyleneacetoaceto*-p-*toluidide* (II; R = *p*-tolyl).—A solution of 3-methyl-4-*p*-toluidinomethylene*iso*oxazolid-5-one (0·5 g.) and *p*-toluidine (0·25 g.) in ethanol (10 ml.) was refluxed for 1 hour, then evaporated to small bulk and acidified with dilute acetic acid; α-p-*toluidinomethyleneacetoaceto*-p-*toluidide* (0·45 g.) separated as a yellow solid and crystallised from ethanol–water as pale lemon-yellow needles, m. p. 156° (Found: C, 73·8; H, 6·4; N, 9·05. $C_{19}H_{20}O_2N_2$ requires C, 74·1; H, 6·55; N, 9·1%).

4-*Acetylpyrazol*-3-*one* (III; R′ = H).—3-Methyl-4-*p*-toluidinomethylene*iso*oxazolid-5-one

(1 g.) in ethanol (10 ml.) was refluxed with hydrazine (0·32 ml. of a 50% aqueous solution) for 1 hour; ammonia was freely evolved and the clear solution when evaporated *in vacuo* gave 4-*acetylpyrazol*-3-*one* (0·5 g.), which separated from water as colourless needles, m. p. 225° (decomp.) (Found: C, 47·8; H, 4·85; N, 22·3. $C_5H_6O_2N_2$ requires C, 47·7; H, 4·8; N, 22·25%). The same compound was obtained from 4-anilinomethylene-3-methyl*iso*oxazolid-5-one and hydrazine.

4-*Acetyl*-1(or 2)-*phenylpyrazol*-3-*one* (III *or* IV; R′ = Ph).—3-Methyl-4-*p*-toluidinomethylene*iso*oxazolid-5-one (1 g.) when similarly treated with phenylhydrazine (0·6 g.) gave 4-*acetyl*-1(or 2)-*phenylpyrazol*-3-*one* (0·7 g.), which separated from water as needles, m. p. 191—192° (decomp.) (Found: C, 65·0; H, 5·2; N, 13·85. $C_{11}H_{10}O_2N_2$ requires C, 65·3; H, 5·0; N, 13·85%).

5-*Acetyl*-2-*phenylpyrimid*-4-*one* (V; R′ = Ph).—Benzamidine hydrochloride hydrate (1 g.) was added to a solution of sodium (0·12 g.) in ethanol (5 ml.), followed by 3-methyl-4-*p*-toluidinomethylene*iso*oxazolid-5-one (1·1 g.). The solution was refluxed for 1 hour; ammonia was liberated and the solution became yellow. An equal volume of water was added to the cooled solution, and a small precipitate filtered off. Acidification of the filtrate with acetic acid gave a granular, pale yellow solid; 5-*acetyl*-2-*phenylpyrimid*-4-*one* (0·5 g.) separated from ethanol as white laths, m. p. 237—241° (decomp.) [Found: C, 67·2; H, 4·75; N, 13·1%; *M* (Rast), 210. $C_{12}H_{10}O_2N_2$ requires C, 67·25; H, 4·7; N, 13·05%; *M*, 214].

5-*Acetyl*-2-p-*methanesulphonylphenylpyrimid*-4-*one* (V; R′ = *p*-Me·SO_2Ph).—3-Methyl-4-*m*-toluidinomethylene*iso*oxazolid-5-one (1·1 g.) and *p*-methanesulphonylbenzamidine (1·2 g.) were refluxed together in ethanol (5 ml.), ammonia being evolved. When cooled, the solution deposited the pyrimidone as the p-*methanesulphonylbenzamidinium* salt (0·7 g.), which separated from ethanol as plates, m. p. 259—260° (decomp.) (Found: C, 51·5; H, 4·7; N, 11·25. $C_{13}H_{12}O_4N_2S$,$C_8H_{10}O_2N_2S$ requires C, 51·4; H, 4·5; N, 11·4%). The salt (0·5 g.) readily dissolved in N-sodium hydroxide (5 ml.), and when the solution was acidified with hydrochloric acid a thick crystalline precipitate appeared; 5-*acetyl*-2-p-*methanesulphonylphenylpyrimid*-4-*one* (0·25 g.) separated as laths (from ethanol), m. p. 275—276° (Found: C, 53·5; H, 4·4; N, 9·45. $C_{12}H_{12}O_4N_2S$ requires C, 53·4; H, 4·15; N, 9·6%).

4-*Acetyl*-2-p-*tolyliso*oxazolid-5-*one* (VI; R = *p*-tolyl).—3-Methyl-4-*p*-toluidinomethylene*iso*oxazolid-5-one (3·8 g.) in ethanol (80 ml.) was treated with N/20-sodium hydroxide (350 ml.), and the solution kept at room temperature (20°) for 30 minutes; during this time a small amount of crystalline precipitate appeared but soon redissolved. The filtered solution when acidified with 2N-hydrochloric acid gave a mass of white needles; 4-*acetyl*-2-p-*tolyliso*oxazolid-5-*one* (1·5 g.) separated from ethanol as needles, m. p. 151—152° (decomp.) [Found: C, 65·8; H, 5·85; N, 6·35%; *M* (Rast), 229. $C_{12}H_{13}O_3N$ requires C, 65·7; H, 5·9; N, 6·4%; *M*, 233], having the solubility and colour reaction described on p. 3429. The same compound was obtained by reaction of 3-methyl-4-*p*-toluidinomethylene*iso*oxazolid-5-one with acetamidine, guanidine, and sodium alkoxides in alcohols, and also in a number of attempted condensations involving the use of sodium alkoxides. When the acetyl*iso*oxazolidone (0·5 g.) was warmed with N-sodium hydroxide (5 ml.) for a short time on the steam-bath, a milky solution was obtained which, when cooled, deposited 4-p-*tolyliminobutan*-2-*one* (VII; R = *p*-tolyl) (0·3 g.); this separated from ethanol–water as laths, m. p. 110—111° (Found: C, 75·2; H, 7·4; N, 7·8. $C_{11}H_{13}ON$ requires C, 75·4; H, 7·5; N, 8·0%). Arylaminomethylene*iso*oxazolones showed no tendency to rearrange in the presence of strong bases; *e.g.*, 3-methyl-4-*p*-toluidinomethylene*iso*oxazol-5-one (1·1 g.) was dissolved in ethanol (10 ml.) containing sodium (0·12 g.), and the solution warmed on the steam-bath for 1 hour then kept overnight. A thick precipitate appeared and was dissolved by addition of an equal volume of water. Acidification of the solution gave the unchanged *iso*oxazolone (0·85 g.) as pale yellow prisms (from ethanol), m. p. 200° (decomp.) unaltered on admixture with an authentic specimen.

4-*Acetyl*-2-*phenyliso*oxazolid-5-*one* (VI; R = Ph).—A solution of 4-anilinomethylene-3-methyl*iso*oxazolid-5-one monohydrate (2·2 g.) in ethanol (10 ml.) containing sodium (0·23 g.) was warmed to 50° for 10 minutes. A yellow turbidity rapidly appeared; the cooled solution was treated with water and a gelatinous precipitate appeared (sodium salt?); this was dissolved by further addition of water (*ca.* 20 ml. in all). The clear brown solution when acidified with acetic acid deposited a mass of crystals; 4-*acetyl*-2-*phenyliso*oxazolid-5-*one* (1 g.) separated from ethanol as laths, m. p. 123—125° (decomp.) [Found: C, 64·15; H, 5·4; N, 7·1%; *M* (Rast), 202. $C_{11}H_{11}O_3N$ requires C, 64·4; H, 5·4; N, 6·85%; *M*, 205]. The *iso*oxazolidone in alcoholic solution gave a red colour with ferric chloride.

Reaction of 3-*Methyl*-4-p-*toluidinomethylene*iso*oxazolid*-5-*one with Sodium Hydrogen Sulphide.*

—(*a*) The *iso*oxazolidone (1 g.) was dissolved in a solution of sodium (0·12 g.) in ethanol (15 ml.) which had been saturated with hydrogen sulphide. After 4 hours at room temperature (25°) dilute acid was added to precipitate the unchanged material (0·9 g.), m. p. 184° (decomp.). (*b*) The experiment (*a*) was repeated but the solution was heated on the steam-bath for 1 hour, during which it rapidly became turbid and dark reddish-brown. To the cooled solution was added dilute acetic acid to precipitate a dark tar which was filtered off; the dark brown filtrate, after 2 hours, deposited a crystalline solid (0·4 g.) which separated from ethanol–water as laths, m. p. 110° alone and when mixed with 4-*p*-tolyliminobutan-2-one, m. p. 110—111°. Attempts to isolate crystalline material from the tar were unsuccessful.

Reaction of 3-*Methyl*-4-p-*toluidinomethylene*isoo*xazolid*-5-*one with Hydroxylamine.*—The *iso*-oxazolidone (2·1 g.) was added to a solution of hydroxylamine hydrochloride (0·7 g.) and sodium (0·23 g.) in ethanol (30 ml.); it readily dissolved and an odour of ammonia soon became noticeable. The mixture was gently warmed on the steam-bath, and ammonia was more freely liberated. After 30 minutes, the solution was filtered from sodium chloride, and the filtrate evaporated to dryness *in vacuo*, to give a pale brown oil which had an odour of *p*-toluidine. The oil was stirred with light petroleum (3 × 20 ml.) and when set aside it soon crystallised. The crystalline mass was lixiviated with water (5 ml.) and filtered, to give a pale yellow solid. The latter was treated with dilute sodium hydroxide (5 ml.) and it partly dissolved. The insoluble residue separated from ethanol–water as plates (0·3 g.), m. p. 149—150°, and may be *dihydro*-3-*methyl*-6-p-*tolyl*-1 : 2 : 6-*oxadiazine* (XII; R = Me, R′ = H, R″ = *p*-tolyl) (Found: C, 69·0; H, 7·25; N, 14·9. $C_{11}H_{14}ON_2$ requires C, 69·45; H, 7·4; N, 14·75%). The oxadiazine (0·1 g.) was dissolved in ether (5 ml.), and concentrated hydrochloric acid (1 drop) added, precipitating a yellow solid; this *hydrochloride* (0·08 g.) separated from ethanol–ether as pale yellow plates, m. p. 212° (decomp.) (Found: C, 58·0; H, 6·5; N, 12·0. $C_{11}H_{14}ON_2$,HCl requires C, 58·25; H, 6·65; N, 12·35%). Acidification of the above alkaline solution precipitated 3-methyl-4-*p*-toluidinomethylene*iso*oxazol-5-one (0·25 g.), which separated from ethanol–water as very pale yellow laths, m. p. 198—199° (decomp.) (Found: N, 13·15. Calc. for $C_{12}H_{12}O_2N_2$: N, 12·95%), not depressed on admixture with an authentic specimen, m. p. 200° (decomp.). The light petroleum extract when evaporated to dryness gave an oil which soon crystallised and was largely *p*-toluidine (0·4 g.). The same compounds were isolated similarly from the reaction of 4-acetyl-2-*p*-tolyl*iso*oxazolid-5-one (VI; R = *p*-tolyl) with hydroxylamine.

Thanks are expressed to Mr. E. Mansberg for help in the preparation of some of the intermediates used in this work and to Dr. E. Challen for the semimicro-analyses.

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660. *The Passivity of Metals. Part XI.* The Anodic Behaviour of Iron Oxide Films.*

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A study has been made of the behaviour of iron, coated with visible oxide film by previous heating in air, when subjected to anodic treatment in dilute sulphuric acid. Measurements have been made of the time needed for the destruction of the oxide film by auto-reduction after interruption of the current; this break-down time (t_b) increases with increase of the time (t_c) during which the current flows before the interruption. The increase in t_b is attributed to the increase in the oxygen-charge built up by the anodic polarisation. The scatter of the results is probably due to intermittent cracking of the film. Similar results have been obtained at different current densities and at different temperatures, although auto-reduction occurs much more rapidly at 24° than at 6°.

EARLIER work (Pryor and Evans, *J.*, 1950, 1259) has attributed the rapid destruction of the films on heat-tinted iron placed in dilute sulphuric or hydrochloric acid to the cell,

* Part X, *J.*, 1949, 3330.

Fe (anode) | acid | Fe_2O_3 (cathode), set up at certain sensitive points; these may be either definite gaps in the film or places rich in lattice defects where iron cations from the metal can migrate outwards through the film substance. The reduction process by the local cells is termed auto-reduction. Powdered ferric oxide placed on mercury, covered with acid and joined by an external wire to an iron anode also dipping into the acid, suffers reductive dissolution in the same way as an oxide film clinging to its iron basis; ferric oxide passes into solution as ferrous ions (*idem*, *ibid.*, p. 1266). The direct attack on the ferric oxide powder (in absence of cathodic polarisation) is much slower (*idem*, *J.*, 1949, 3330); likewise, ferric oxide films, after separation from the metallic basis, can be kept in acid for long periods without dissolution. Heat-tinted iron, which, when placed in dilute sulphuric acid, loses its colour within a few seconds, retains the colour unchanged for 24 hours if chromic acid also is present in sufficient amount (Evans, *J.*, 1930, 481). In the presence of chromic acid, a powerful oxidising agent, the ferric oxide film escapes destruction; presumably any cathodic action would reduce chromic acid in preference to ferric oxide.

It would seem likely that high-pressure oxygen (such as can be obtained by anodic action under conditions where there is appreciable oxygen overvoltage) might prevent the destruction of the films, acting like chromic acid. If, however, the film contains a metal, such as chromium, whose tervalent ions are not easily reduced (Latimer, "Oxidation Potentials," Prentice-Hall, 1938), ordinary (low-pressure) oxygen dissolved in the acid might suffice. It is possible that the invisible film on stainless steel is protected in this way by low-pressure oxygen, which prevents reductive dissolution, allows the film to be repaired at gaps, and to be thickened at points rich in lattice defects; austenitic stainless steel resists dilute sulphuric acid in the presence of oxygen, but not in its absence—a matter now under experimental study.

A heat-tinted iron electrode, plunged into dilute sulphuric acid, in such a way that it is subjected to anodic action from the instant of immersion, immediately becomes passive, provided the current density is sufficiently high; oxygen is evolved, the interference colours remain unchanged, and the iron is practically unattacked (Evans, *J.*, 1930, 482). If the current is interrupted for more than a few seconds, the film is destroyed and the colours disappear; when the current is again turned on, the iron behaves as an active anode, passing easily into solution. A very short interruption is, however, possible without loss of passivity or destruction of the film. In the experiments of 1930, the period of interruption which could be tolerated without loss of passivity seemed to increase with increase of time of current flow—as though the oxide film had become more protective as the anodic treatment was prolonged; however, the relationship was not studied.

The temporary immunity obtained after short interruptions may tentatively be attributed to the oxygen-charge left by the anodic treatment, since oxygen should suffer reduction before the ferric oxide itself is destroyed. If so, a detailed study of the phenomenon might give information useful in the study of the immunity of stainless steel, where traces of oxygen in the liquid suffice to maintain passivity. Hence, the present research was undertaken into the relation between the time of current flow (t_c) and the time of auto-reduction or breakdown of the film (t_b).

Experimental

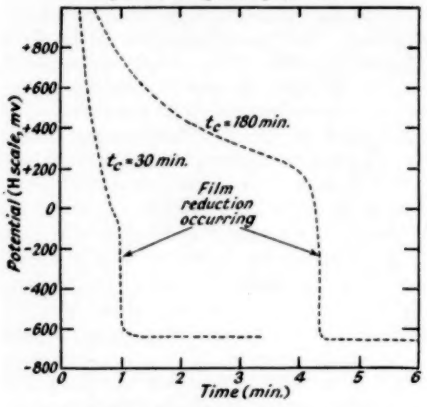
Materials.—Swedish iron sheet, 0·16 mm. thick, was used, containing C, 0·034%; Si, 0·010%; Mn, 0·145%; S, 0·015%; P, 0·032%; Ni, 0·030%; Cr, 0·007%; Mo, 0·005%; V, 0·010%; Ti, 0·010%; Al, 0·006%; Sn, 0·006%; W, 0·050%; Cu, 0·010%; Pb, 0·001%. It contained plentiful inclusions of magnetite (Evans, *Nature*, 1949, **164**, 909.)

Preparation of Specimens.—Pieces of iron measuring 1·4 × 3·0 cm. were degreased in benzene, the excess being taken up with filter-paper, abraded with 3/0 emery paper, again degreased, and dried. The specimens were heated in an electric air-oven, being supported in a rack made by cutting slots in an aluminium block 20 × 2 × 2 cm. The iron specimens rested in the slots so that they remained freely accessible to the air and all at the same temperature; a "Sunvic" thermo-electric regulator was used to maintain the oven at 235° ± 2° and the specimens remained at this temperature for 34 hours. A first-order dark-blue interference colour was produced evenly over the whole area—suggesting a uniform film-thickness; the film thus obtained is

largely composed of rhombohedral α-ferric oxide (Winterbottom, *J. Iron Steel Inst.*, 1950, **165**, 9; Pryor and Evans, *J.*, 1950, 1259; "Chemistry Research," 1950, D.S.I.R., Teddington). After cooling, part of each specimen was masked with polystyrene, dissolved in xylene, and then a layer of paraffin was applied molten, in order to protect the water-line zone; an area of oxide 1·4 × 1·4 cm. was left exposed on each side.

Apparatus.—A tinted specimen served as anode, and an untinted piece of iron as cathode. Before the experiment they were both clamped to a frame consisting of two parallel strips of

FIG. 1. *Typical time–potential curves obtained after interruption of current.*



0·1M-*Sulphuric acid; C.D.* 6 *ma/sq. cm.; temperature* 6° ± 1°.

FIG. 2. *Diagram of apparatus used for measuring the variation of* t_b *with* t_c.

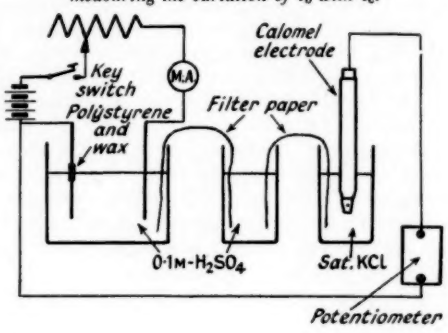


FIG. 3. *Relationship of* t_b *and* t_c; *C.D.* 6 *ma/sq. cm.,* 0·1M-*sulphuric acid at* 6°.

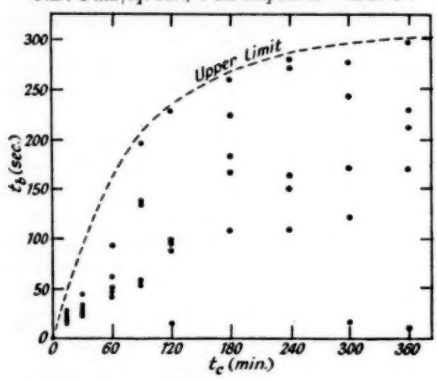
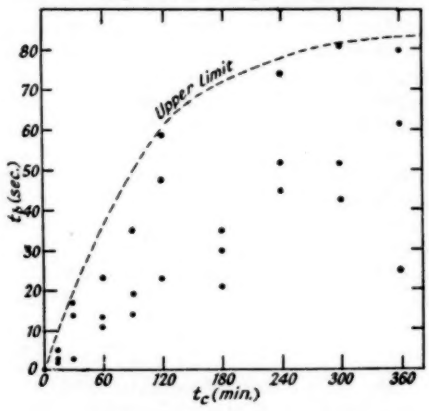


FIG. 4. *Relationship of* t_b *and* t_c; *C.D.* 6 *ma/sq. cm.,* 0·1M-*sulphuric acid at* 24°.



fibre rigidly connected together (Evans, *J. Soc. Chem. Ind.*, 1928, **47**, 73T, illustration). The anode and cathode were connected by flexible wire through a variable resistance, key, and milliammeter to accumulators; the distance between the two electrodes was 3·0 cm. When the frame was lowered, the current flowed from the instant when the electrodes entered the acid.

Method.—The time of breakdown of the film after a certain period of anodic treatment was measured by a method involving changes in the single-electrode potential of the iron. Fig. 1 shows typical time–potential relationships for two specimens after the current which had previously flowed for 30 and 180 minutes, respectively, had been interrupted. The single-electrode potential of iron changes sharply when the oxide film is reduced, dropping some 700 mv within a second. If the polarising current is restarted before the sudden drop, the electrode

remains passive and oxygen is again evolved; if it is restarted after the drop, the iron corrodes actively and no oxygen appears. The sudden drop also corresponds with the disappearance of the interference colour.

The circuit used is shown in Fig. 2. Potential measurements were made with a valve-potentiometer against a saturated calomel reference electrode in saturated potassium chloride. The potentiometer was adjusted to a potential reading of −400 mv, a value slightly above that of active iron. In each experiment the specimen was polarised anodically in 0·1M-sulphuric acid for a known period of time (t_c), and then the polarising current was interrupted. When the film suffered auto-reduction, the needle of the potentiometer swung across the scale and the time between the interruption and the swing was taken to correspond to the time of breakdown (t_b).

Results.—(1) *Dependence of* t_b *on* t_c. Two series of experiments were carried out in which the t_b values for specimens anodically polarised for periods ranging up to 360 minutes were measured. In both, 0·1M-sulphuric acid containing dissolved oxygen was used; the temperature of the acid was maintained at 6°±1° in the first series and at 24°±1° in the second. The polarising current density, based on apparent area, was kept constant at 6 ma/sq. cm. in each case. The results are shown in Figs. 3 and 4.

The time of breakdown increases significantly with increasing time of anodic pretreatment. There is, however, a wide scatter of t_b values for any given t_c time. Despite the scatter, there appears to be an upper limit to the t_b value possible for any given t_c. The upper limiting value of t_b increases with t_c, the curve being roughly asymptotic. It seemed possible that the low and

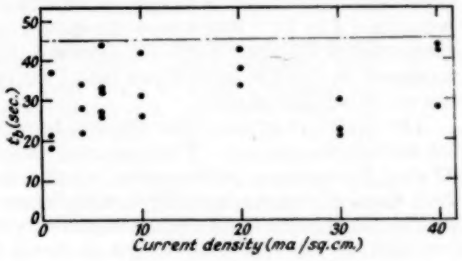


FIG. 5. *Values of* t_b *after* 30 *mins.' polarisation at various current densities, in* 0·1M-*sulphuric acid at* 6°.

the high values might be given by specimens coming from different parts of the original iron sheet from which the specimens had been cut; an enquiry into this matter showed no correlation between the t_b values and position on the original sheet.

(2) *Effect of temperature.* The increase of t_b with t_c is significant at both the temperatures studied and the shapes of the "upper limiting" curves are similar. However, the t_b values obtained at 24° for any given t_c are considerably lower than the t_b values obtained at 6°. The increase in auto-reduction rate with temperature confirms earlier observations (Pryor and Evans, *J.*, 1950, 1259).

(3) *Effect of current density.* A series of experiments were carried out in order to discover whether the current density used for the anodic polarisation affects the time of breakdown. The t_c period was fixed at 30 minutes and, 0·1M-sulphuric acid being used at 6°±1°, the t_b values were measured for apparent current densities ranging from 1 to 40 ma/sq. cm. Specimens introduced at current densities below 1 ma/sq. cm. suffered auto-reduction at once. The results are shown in Fig. 5 and indicate that t_b does not increase with increase in the current strength during the t_c period.

DISCUSSION

During anodic treatment, the blue interference colour of the α-ferric oxide changes to a pale yellow after a t_c period exceeding approximately 2 hours. When the current is interrupted after such a t_c time, the colour of the specimen changes uniformly and rapidly as auto-reduction occurs; the colour of the specimen first darkens to the original blue and then the whole sequence of first-order tints appears in the reverse order as film-thinning proceeds. Apparently some slow film-thickening is occurring during the anodic polarisation, the pale colour just mentioned corresponding to a film giving the second-order yellow.

In the absence of applied current, auto-reduction of the oxide film is due to local cells

Fe|acid|Fe_2O_3. The anodes are points in the film where metal cations can readily pass through, either because the film is thin or because it is in a state of atomic disarray; the thin places may be the sites of old cracks which have been partly healed. Whilst the specimen is undergoing anodic treatment with evolution of oxygen, any cations emerging at sensitive points are arrested and used to provide oxide for film repair, as in dry oxidation. Any fresh defects are blocked with oxide as they appear—explaining the slow thickening of the film. When, however, the current has been interrupted any fresh discontinuities will permit cations to enter the liquid, and this anodic reaction must be accompanied by cathodic destruction of the film at points immediately adjacent, so that the discontinuity spreads rapidly.

α-Ferric oxide is believed to be a semi-conductor of the metal-excess type, containing vacant sites in the oxygen lattice (Pfeil, *J. Iron Steel Inst.*, 1929, **119**, 501; **123**, 237; Garner, *Chem. and Ind.*, 1947, 132; Bevan, Shelton, and Anderson, *J.*, 1948, 1729). It has been further shown that the composition of the oxide varies with the effective oxygen pressure of the phase with which it is in contact; probably, during prolonged anodic treatment with oxygen evolution, the outer portion of the film will acquire an oxygen content considerably higher than that of similar oxide which has not experienced anodic pretreatment. On interruption of the current, the excess of oxygen must be removed from the whole surface by cathodic action before the localised reduction of the oxide proper can occur close to the discontinuities. This must be the case since the potential of the ferric oxide containing excess of oxygen exceeds that of the ferric oxide which has lost most of its excess (see Fig. 1). When once the excess of oxygen has been exhausted, the reductive dissolution of the oxide itself will start and this will be localised owing to considerations of resistance, so that the area of bare metal will rapidly increase. Thus film-destruction, once started, is self-stimulating.

The charge of excess of oxygen will become greater with increasing t_c and, therefore, t_b will also increase with t_c. The content of excess of oxygen in the film is apparently limited. (It may, for instance, be determined by the number of vacant anion sites near the surface. Once these sites have been filled, replenishment by the diffusion of vacant sites from the interior of the oxide to the surface will be very slow at the temperatures under consideration. Provided the rate of anodic oxygen discharge is ample to fill the vacant sites as they reach the surface, the value of the current density should be unimportant—thus explaining the results of Fig. 5.) After a certain time of anodic treatment, the greatest possible oxygen charge will be approached. Thus, there is a limiting value of t_b which can never be exceeded, explaining the asymptotic shape of the curves in Figs. 3 and 4.

The scatter of t_b values obtained at a fixed t_c value remains to be explained. It was observed that all the films were immediately reduced if touched with an iron wire. Hence the premature destruction of the oxide films on certain specimens may be accounted for by the formation of an actual crack in the film, sufficient to allow acid to come into contact with metallic iron. Such cracking is not improbable. Earlier work (Evans, *Nature*, 1946, **157**, 732) has indicated the presence of weak points in films formed at low temperatures in air; they were repaired by fresh oxidation but others are continuously and spontaneously appearing. Presumably the defects arise from internal stresses, the presence of which is suggested by the wrinkling or curling when the films are transfered to vaseline-coated glass (Evans, Symposium on Internal Stresses in Metals and Alloys, Inst. Met., October 1947, p. 291). The irreproducibility of the results is an indication that the disastrous cracking occurs only at intervals wide in time and space. If the number of cracks to be expected in a specimen area during a time typical of t_b were large, Bernouilli's principle would predict reproducibility. Any such cracks occurring during the t_c period would be repaired without the reductive destruction of the main film. Even a crack formed just after interruption of the current might be repaired, since there would still be a high oxygen charge in the outer layers of the oxide and dissolved oxygen in the acid. This is suggested by the fact that few points are found in the lower half of the area below the limiting curve. But any crack produced during the period of interruption, which cannot be repaired by oxygen existing in or around the oxide film, causes rapid and self-stimulating autoreduction.

The interpretation offered above is advanced tentatively, but it appears to cover the facts.

Conclusions.—The oxide film on iron is immediately auto-reduced by dilute sulphuric acid; anodic polarisation preserves the film and oxygen is evolved. During the anodic treatment, the film acquires a charge of excess of oxygen in its outer layers which (like chromic acid in earlier work) must be removed from the whole surface before localised reduction of the ferric oxide can start. Scatter of the results is attributed to periodic cracking of the film which causes premature auto-reduction.

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661. *Formation of Organo-phosphorus Compounds by the Reaction of Alkyl Chlorides with Phosphorus Trichloride in the Presence of Aluminium Chloride.**

By A. M. KINNEAR and E. A. PERREN.

Many alkyl chlorides condense with phosphorus trichloride and aluminium chloride to form liquid or solid complexes, which when decomposed with water under controlled conditions give good yields of alkylphosphonyl dichlorides R·$POCl_2$. *n*-Alkyl chlorides containing <3C give the corresponding *sec.*-alkylphosphonyl dichloride. By treatment with hydrogen sulphide the aluminium chloride complexes give successively alkylthiophosphonyl dichlorides R·$PSCl_2$ and dithiophosphoalkanes R·PS_2. Evidence that the complexes are salt-like substances $[R{\cdot}PCl_3]^+[AlCl_4]^-$ is presented. Some reactions between alkyl chlorides and derivatives of phosphorus trichloride are also described.

CLAY (*J. Org. Chem.*, 1951, **16**, 892) prepared alkylphosphonyl dichlorides R·$POCl_2$ by treating alkyl chlorides with phosphorus trichloride in the presence of aluminium chloride and decomposing the resulting complex with cold concentrated hydrochloric acid. This reaction has been observed independently by the present authors.

Ten alkyl chlorides, as well as *cyclo*hexyl and benzyl chloride, reacted readily with phosphorus trichloride and aluminium chloride to give complexes which on treatment with water gave good yields of alkylphosphonyl dichlorides. *n*-Propyl, *n*-butyl, and *iso*butyl chloride yielded products identical with those obtained from *iso*propyl, *sec.*-butyl, and *tert.*-butyl chloride respectively with no trace of un-isomerised products. Although this isomerisation is somewhat analogous to that occurring when alkyl chlorides are condensed with benzene by the Friedel–Crafts reaction, the parallel is not complete, since, for instance, in the reaction between *n*-propyl chloride and benzene a mixture of *n*- and *iso*-propylbenzene is always formed (Ipatieff, Pines, and Schmerling, *ibid.*, 1940, **5**, 253).

Vinyl chloride failed to react but allyl chloride gave a fair yield of allylphosphonyl dichloride ($CH_2{:}CH{\cdot}CH_2{\cdot}POCl_2$) (contrast the isomerisation during Friedel–Crafts condensation).

Methylene chloride, chloroform, and carbon tetrachloride gave good yields of chloro-, dichloro-, and trichloro-methylphosphonyl dichloride respectively. Carbon tetrachloride was nearly as reactive as the alkyl monochlorides, but chloroform required refluxing for some hours to ensure complete reaction, and methylene chloride required heating at 100° in a closed vessel for 24 hours. Benzylidene dichloride and benzotrichloride also reacted similarly, provided that conditions were adjusted to minimise Friedel–Crafts condensation. On treatment with aniline the carbon tetrachloride derivative gave trianilinophosphine

* Cf., in part, B.P. Applns. 11,956/1948, 26,475/1951.

oxide, $(NHPh)_3PO$, instead of the dianilide afforded by most of the phosphonyl dichlorides, this being an example of the readiness (cf. Kamai, *Compt. rend. Acad. Sci. U.R.S.S.*, **1947**, **55**, 219) with which the carbon–phosphorus bond, normally very stable, breaks when the carbon atom is attached to three chlorine atoms.

Ethylene dichloride and, especially, ethylidene dichloride, give good yields of phosphonyl dichlorides. *s*-Tetrachloroethane appeared to be quite unreactive and penta- and hexachloroethane, although appearing to form complexes, yielded no phosphonyl chloride. Instead in each case a quantity of phosphorus oxychloride was produced. Tri- and tetrachloroethylene appeared moderately reactive but, although the former yielded a small quantity of a phosphonyl chloride, the latter again produced only phosphorus oxychloride.

Attempts to make bisphosphonyl derivatives failed. Even 1 : 5-dichloropentane gave 4-chloro-1-methylbutylphosphonyl dichloride $CH_2Cl\cdot[CH_2]_2\cdot CHMe\cdot POCl_2$ with no trace of higher-boiling material.

A number of hydrocarbons substituted by bromine and fluorine were investigated. With the exception of chlorotrifluoromethane, which proved entirely unreactive, all gave products identical with those obtained from the corresponding chlorohydrocarbons, *e.g.*, chlorodifluoromethane gave dichloromethylphosphonyl dichloride.

Clay (*loc. cit.*) gives formula (I) for the complex formed in excellent yield by heating together equimolecular proportions of alkyl chloride, phosphorus trichloride, and aluminium chloride. This is borne out by the following observations: (1) Complexes, which although different in crystalline form were similar to the ethyl chloride complex in being crystalline solids of high melting point and in giving ethylphosphonyl dichloride on hydrolysis, were prepared either by adding aluminium chloride to ethylphosphorus tetrachloride $Et\cdot PCl_4$ or by passing chlorine into the complex of ethyldichlorophosphine $Et\cdot PCl_2$ and aluminium chloride. (2) The ethyl chloride complex was stable when heated for long periods with chlorohydrocarbons, *e.g.*, carbon tetrachloride. (3) Solutions of the complex in methylene chloride were readily electrolysed yielding, as the anode, aluminium chloride and, at the cathode, a product which although not precisely identified had the properties of an alkyldichlorophosphine $R\cdot PCl_2$. Support for this formula is also afforded by the existence of the analogous tetraphenylarsonium salt $[Ph_4As]^+[AlCl_5Br]^-$ which was shown by Lyon and Mann (*J.*, 1942, 666) to be formed by the action of bromobenzene on trichloro(triphenylarsine)aluminium ($Ph_3As\rightarrow AlCl_3$). The latter aluminium compound is a crystalline solid easily prepared by the addition of the two constituents. Although phosphorus trichloride and aluminium chloride do not give an analogous easily isolated compound, it is possible that a small degree of combination occurs, possibly in an equilibrium reaction. For the formation of (I) Clay suggested that the first stage was $RCl + PCl_3 \rightleftharpoons R\cdot PCl_4$. An alternative now proposed is:

$$PCl_3 + AlCl_3 \rightleftharpoons PCl_3,AlCl_3$$
$$PCl_3,AlCl_3 + RCl \longrightarrow [RPCl_3]^+[AlCl_4]^- \quad (I)$$

There is, however, insufficient evidence at present to decide between the two mechanisms. The hydrolysis mechanism suggested by Clay does not appear to be entirely satisfactory since it involves combination of a chlorine ion set free by the action of water on $[AlCl_4]^-$ with $[R\cdot POCl]^+$ produced by the action of water on $[R\cdot PCl_3]^+$. An alternative mechanism, as follows, appears more probable:

$$[R\cdot PCl_3]^+[AlCl_4]^- + H_2O \longrightarrow HAlCl_4 + R\cdot PCl_3\cdot OH \longrightarrow R\cdot POCl_2 + HCl$$

It appeared to be of interest to investigate the behaviour of the complexes with a reagent less vigorous than water. Hydrogen sulphide was found to react slowly with (I; R = Et) at about 130° with the evolution of hydrogen chloride. When the reaction was allowed to go to completion (several days), the main product after treatment with water was a colourless crystalline solid, $C_2H_5PS_2$, m. p. 157°, which in warm water gave a colourless solid, C_2H_5POS, m. p. 54—55°. It is doubtful whether the two compounds have these simple constitutions since the infra-red spectrum of the oxygen compound (personal communication from Mr. L. C. Thomas) does not contain the strong absorption band characteristic of the P=O grouping (Meyrick and Thompson, *J.*, 1950, 229), and they have thus

probably cyclic structures. It is convenient, however, to refer to them as dithiophosphoethane (II) and thiophosphoethane (III) respectively. By stopping the reaction between (I) and hydrogen sulphide before completion, ethylthiophosphonyl dichloride (IV) was obtained. This sequence of reactions, by analogy with the hydrolysis mechanism already suggested, may proceed as follows :

$$[EtPCl_3]^+[AlCl_4]^- \xrightarrow{H_2S} Et{\cdot}PCl_2{\cdot}SH + HAlCl_4$$

$$\downarrow$$

$$\text{(IV)}\quad Et{\cdot}PSCl_2 + HCl$$

$$Et{\cdot}PSCl_2 \xrightarrow{H_2S} HCl + \underset{\text{(V)}}{Et{\cdot}PS(SH)Cl} \longrightarrow \underset{\text{(II)}}{Et{\cdot}PS_2} + HCl$$

$$\downarrow EtOH \qquad\qquad \downarrow H_2O$$

$$\text{(VI)}\quad Et{\cdot}PS(SH){\cdot}OEt \qquad\qquad Et{\cdot}POS \quad \text{(III)}$$

A derivative, *O*-ethyl hydrogen ethyldithiophosphonate (VI), of the postulated intermediate (V) was obtained by treating the mixed reaction products with ethyl alcohol.

A few experiments were performed to ascertain to what extent the ability to condense with alkyl chlorides was affected by substitution of the chlorine atoms in phosphorus trichloride by other atoms or groups. Dichlorophosphinous esters (VII) and alkyl chlorides in the presence of aluminium chloride readily gave alkylphosphonyl dichlorides $R{\cdot}POCl_2$. In this case the mechanism cannot have been that suggested for the phosphorus trichloride reactions, since this would have led to an ester of an alkylchlorophosphinic acid $R''{\cdot}PO(OR')Cl$; it must be assumed that the following reactions take place :

$$\text{(VII)}\quad R'O{\cdot}PCl_2 + R''Cl \xrightarrow{AlCl_3} [R'O{\cdot}PR''Cl_2] \longrightarrow R''POCl_2 + R'Cl$$

This mechanism conforms closely to that of an Arbusov rearrangement (von Kosopaloff, " Organophosphorus Compounds," J. Wiley & Son, New York, 1950, p. 121) which involves the reaction of an organic halide with a tervalent phosphorus ester to give a phosphine oxide :

$$R^1O{\cdot}PR^2R^3 + R^4X \longrightarrow [R^1O{\cdot}PR^2R^3R^4X] \longrightarrow O{:}PR^2R^3R^4 + R^1X$$

This reaction has not hitherto been known to occur when R'' or R''' = halogen and in the example just described it is evident that it is promoted by the aluminium chloride. When a *n*-alkyl halide takes part in a normal Arbusov rearrangement it does not undergo isomerisation and it is therefore of interest that *n*-propyl chloride produced *iso*propylphosphonyl dichloride. (Ethers also react with phosphorus trichloride and aluminium chloride to give alkylphosphonyl dichlorides, the ether presumably first reacting with phosphorus trichloride to give a dichlorophosphinous ester and an alkyl chloride, which then undergo the rearrangement just described.)

Ethyldichlorophosphine, in contrast to phosphorus trichloride, combines vigorously with aluminium chloride, and the product appears to react with ethyl chloride. No recognisable products, however, were isolated on hydrolysis. Although ethyl diethylphosphinate, $Et_2PO{\cdot}OEt$, was obtained by treatment of the reaction product with ethyl alcohol, it is probable that this arose by the formation of diethyl ethylphosphonite $Et{\cdot}P(OEt)_2$, from unchanged ethyldichlorophosphine, which then underwent Arbusov rearrangement in the presence of ethyl chloride.

Experimental

The following procedures were used for the formation of aluminium chloride complexes (see Table). In each case the reaction was continued until all aluminium chloride had gone into solution.

A. The alkyl halide, phosphorus trichloride (or derivative), and aluminium chloride were mixed in that order and in the proportions indicated and shaken at room temperature, if necessary in a sealed vessel.

B. As A, except that the mixture was heated on the water-bath for a further period.

C. Aluminium chloride was suspended by continuous stirring in phosphorus trichloride,

	Reagents			Mol. proportions			Reaction conditions		Product		
No.[a]	Alkyl halide	PXX'Cl X =	X' =	RCl	PXX'Cl	$AlCl_3$	Complex formation	Hydrolysis, mols. H_2O	R in R·POCl$_2$	B. p./mm.	Yield, calc. on PXX'Cl, %
1	MeCl	Cl	Cl	1·5	1·0	1·1	A (64 hrs.)	14	Methyl	{ 162°/760 m. p. 33°	68
2	EtCl	Cl	Cl	0·35	0·25	0·27	B (½ hr. ½ hr.)	2·8	Ethyl	34°/3	82
3	Pr^{i}Cl	Cl	Cl	0·30	0·25	0·50	A (1 hr.)	See note	*iso*Propyl	35·5°/1·5	70
4	Pr^{n}Cl	Cl	Cl	0·25	0·25	0·50	B (1 hr. 1 hr.)	2·5	,,	35°/0·5	90
5	CHMeEtCl	Cl	Cl	0·25	0·25	0·50	A (12 hrs.)	4·5	sec.-*Butyl*	59°/3	83
6	Bu^{n}Cl	Cl	Cl	0·25	0·25	0·50	A (12 hrs.)	4·5	,,	57°/2	93
7	Bu^{t}Cl	Cl	Cl	0·32	0·25	0·25	A (10 mins.)	3·5	*tert.*-Butyl	m. p. 110°	81
8	$CHMe_2$·CH_2Cl	Cl	Cl	0·25	0·25	0·5	A (1 hr.)	5·5	,,	m. p. 110°	92
9	CH_3·$[CH_2]_{15}$·Cl	Cl	Cl	0·15	0·30	0·30	A (2 hrs.)	3·5	1-*Methylpentadecyl*	165°/1	60
10	$C_6H_{11}Cl$ [b]	Cl	Cl	0·25	0·50	0·50	A (15 mins.)	5·0	*cyclo*Hexyl	90°/1	82
11	C_6H_5·CH_2·Cl	Cl	Cl	0·25	1·1	0·5	C (½ hr. 40°)	4·5	*Benzyl*	{ 130°/2 m. p. 57·5°	62
12	CH_2:CHCl	Cl	Cl	—	1·1	0·5	F (1½ hrs. 40–50°)	5·0	1-*Chloroethyl*	80—84°/15	Trace
13	CH_2:CH·CH_2Cl	Cl	Cl	0·25	1·0	0·5	C (½ hr. 40—50°)	4·5	*Allyl*	55°/3	53
14	CH_2Cl_2	Cl	Cl	1·0	1·0	1·0	D (24 hrs.)	11	*Chloromethyl*	50/0·5	85
15	$CHCl_3$	Cl	Cl	0·5	0·25	0·5	E (10 hrs.)	3·0	*Dichloromethyl*	79/9	63
16	CCl_4	Cl	Cl	0·35	0·25	0·25	E (1 hr.)	3·0	*Trichloromethyl*	m. p. 156°	85
17	$(CH_2Cl)_2$	Cl	Cl	0·25	0·5	0·5	E (45 min.)	3·5	2-Chloroethyl	77°/6	58
18	CH_3·$CHCl_2$	Cl	Cl	0·25	0·5	0·5	A (1 hr.)	3·5	1-Chloroethyl	57°/3	75
19	CHCl:CCl_2	Cl	Cl	0·25	0·25	0·25	D (12 hrs.)	2·0	2 : 2 : 2-*Trichloroethyl*	65—66°/1	20
20	C_6H_5·$CHCl_2$	Cl	Cl	0·25	1·0	0·5	C (½ hr. reflux)	3·5	α-*Chlorobenzyl*	{ 132°/2 m. p. 48°	40
21	C_6H_5·CCl_3	Cl	Cl	0·25	1·0	0·5	E (1½ hrs.)	4·5	αα-*Dichlorobenzyl*	114—120°/2	10
22	CH_2Cl·$[CH_2]_2$·CH_2Cl	Cl	Cl	0·25	0·25	0·25	E (½ hr.)	3·0	4-*Chloro*-1-*methylbutyl*	112—123°/1	15
23	CHF_2Cl	Cl	Cl	—	0·25	0·5	F (60°)	4·5	Dichloromethyl	67—70°/1	40
24	CF_2Cl_2	Cl	Cl	—	0·5	0·5	F (60°)	4·5	Trichloromethyl	m. p. 157—158°	50
25	CH_2F·CH_2Cl	Cl	Cl	0·21	0·5	0·5	E (1 hr.)	3·5	2-Chloroethyl	63°/3	35
26	CH_3·$CFCl_2$	Cl	Cl	0·25	0·25	0·5	A (1½ hrs.)	4·5	1 : 1-*Dichloroethyl*	m. p. 147—150°	?
27	CH_2Br_2	Cl	Cl	0·25	0·5	0·5	E (3½ hrs.)	4·5	Chloromethyl	66°/3	35
28	CH_2ClBr	Cl	Cl	0·25	0·5	0·5	E (10 hrs.)	5·0	,,	58°/2	35
29	CCl_2Br	Cl	Cl	0·25	0·25	0·5	E (2 hrs.)	4·5	Trichloromethyl	m. p. 152—162°	90
30	EtCl.	F	Cl	0·5	0·25	0·3	A (6 days)	2·0	Ethyl	50—51°/6	22
31	EtCl	F	F	0·5	0·20	0·20	A (6 days)	2·0	,,	88°/30	15
32	EtCl	Et	Cl	0·25	0·25	0·5	A (12 hrs.)	See note	—	—	—
33	Pr^{i}Cl	Et	Cl	0·25	0·25	0·25	A (1 hr.)	3	See note	143°/1	13 g.
34	EtCl	OEt	Cl	0·25	0·25	0·25	D (5 hrs.)	See note	—	—	—
35	Pr^{n}Cl	Et	Cl	0·30	0·25	0·25	D (1 hr.)	2·5	*iso*Propyl	62°/2	45
36	Bu^{t}Cl	OPr^i	Cl	0·16	0·16	0·16	E (½ hr.)	2·0	*tert.*-Butyl	m. p. 110°	75

[a] For notes see p. 3442.

[b] *cyclo*Hexyl.

	Product					Derivative					
		Found, %		Required, %				Found, %		Required, %	
No.	Formula	C	H	C	H		M. p.	Formula	C	H	C	H
1	—	—	—	—	—	*Dianilide*	156—157°	$C_{13}H_{15}ON_2P$	63·2	6·3	63·4	6·4
2	—	—	—	—	—	*Dianilide*	148—149	$C_{14}H_{17}ON_2P$	63·0	6·75	64·6	6·6
						Diethyl ester	b. p. 65°/4 mm.	$C_6H_{15}O_3P$	43·8	9·1	43·4	9·1
3	$C_3H_7OCl_2P$	22·7	4·4	22·4	4·4	*Dianilide*	199—200°	$C_{13}H_{15}ON_2P$	66·0	7·2	65·7	7·0
4	—	—	—	—	—	Dianilide	199—201	—	—	—	—	—
5	—	—	—	—	—	*Dianilide*	152—153	$C_{16}H_{21}ON_2P$	67·0	7·5	66·8	7·4
6	—	—	—	—	—	Dianilide	152—153	—	—	—	—	—
7	—	—	—	—	—	*Dianilide*	256—257	$C_{16}H_{21}ON_2P$	66·7	7·3	66·8	7·4
8	—	—	—	—	—	Dianilide	256—257	—	—	—	—	—
9	$C_{16}H_{33}OCl_2P$	55·5	9·8	56·0	9·7	—	—	—	—	—	—	—
10	$C_6H_{11}OCl_2P$	35·4	5·7	35·8	5·5	*Dianilide*	229—230	$C_{18}H_{22}ON_2P$	67·6	7·6	68·8	7·4
11	—	—	—	—	—	*Dianilide*	185—186	$C_{19}H_{19}ON_2P$	70·1	5·9	70·8	5·9
12	—	—	—	—	—	*Dianilide*	152—153	$C_{14}H_{16}ON_2ClP$	55·7	5·7	57·1	5·5
13	$C_2H_4OCl_2P$	22·7	3·2	22·7	3·2	*Dianilide*	136—137	$C_{15}H_{17}ON_2P$	67·1	6·55	66·2	6·3
						Dianilide	97—125	$C_{13}H_{14}ON_2ClP$	56·3	5·5	55·6	5·0
14	CH_3OCl_2P	7·46	1·4	7·2	1·2	Chloromethyl-phosphonic acid	89—90	—	—	—	—	—
							—	—	—	—	—	—
						Aniline salt	199—201	$C_7H_{11}O_3NClP$	37·9	5·2	37·6	5·2
15	—	—	—	—	—	*Dianilide*	176—177	$C_{13}H_{12}ON_2Cl_2P$	49·5	4·2	49·6	4·2
16	—	—	—	—	—	*Anilide*	124—125	$C_7H_6ONCl_4P$	28·8	2·3	28·8	2·1
17	$C_2H_4OCl_2P$	13·7	2·5	13·2	2·2	*Trianilide*	166—167	$C_{20}H_{22}ON_3P$	68·6	6·6	68·4	6·3
	—	—	—	—	—	Dianilide	170	$C_{14}H_{16}ON_2ClP$	57·2	5·7	57·1	5·5
18	—	—	—	—	—	*Dianilide*	154—155	$C_{14}H_{16}ON_2ClP$	57·5	5·7	57·1	5·5
19	—	—	—	—	—	*Anilide*	105—106	$C_8H_8ONCl_4P$	31·3	2·95	31·2	2·6
20	$C_7H_4OCl_2P$	35·2	2·8	34·5	2·5	—	—	—	—	—	—	—
21	$C_7H_8OCl_2P$	31·9	2·1	30·2	1·8	—	—	—	—	—	—	—
22	$C_5H_{10}OCl_2P$	28·0	4·6	26·9	4·5	—	—	—	—	—	—	—
23	$CHOCl_4P$	6·4	0·7	6·0	0·5	Dianilide	174—175	$C_{13}H_{12}ON_2Cl_2P$	49·6	4·2	49·6	4·2
24	—	—	—	—	—	Anilide	124	$C_7H_6ONCl_4P$	28·7	2·3	28·8	2·1
25	$C_2H_4OCl_2P$	13·7	2·4	13·2	2·2	Dianilide	170	—	—	—	—	—
26	$C_2H_3OCl_4P$	11·6	1·7	11·1	1·4	—	—	—	—	—	—	—
27	CH_3OCl_2P	7·0	1·3	7·2	1·2	Phosphonic acid	83—87	—	—	—	—	—
						Aniline salt	198—200	—	—	—	—	—
28	CH_3OCl_2P	7·8	1·6	7·2	1·2	Aniline salt	198—200	—	—	—	—	—
30	—	—	—	—	—	Dianilide	148	—	—	—	—	—
31	—	—	—	—	—	Dianilide	148	—	—	—	—	—
32	—	—	—	—	—	*Ethyl diethylphosphinate*	b. p. 68°/1 mm.	$C_6H_{15}O_2P$	46·0	10·1	48·0	10·1
33	—	43·1	9·6	—	—	—	—	—	—	—	—	—
34	—	—	—	—	—	Diethyl ethylphosphonate	67°/2 mm.	$C_6H_{15}O_3P$	42·5	9·3	43·3	9·1
35	—	—	—	—	—	Dianilide	199—200°	—	—	—	—	—
36	—	—	—	—	—	Dianilide	256—257	—	—	—	—	—

Notes on Table.—(2) Found: Cl, 48·3. $C_2H_5OCl_2P$ requires Cl, 48·3%. The diethyl ester was obtained in 92% yield (calc. on phosphorus trichloride) directly from the complex by the method described below.

(3) The reaction product was stirred vigorously with carbon tetrachloride (800 ml.) and the suspension poured through several kg. of crushed ice.

(3) and (4) The dianilides when mixed had undepressed m. p. The dianilide of *n*-propylphosphonic acid prepared from *n*-propyl bromide *via* an Arbusov rearrangement has m. p. 150° (Ford-Moore, personal communication).

(5) and (6) The dianilides were identical (m. p. of mixture not depressed). The *n-butylphosphonyl dianilide* (Found: C, 66·1; H, 7·2. $C_{16}H_{21}ON_2P$ requires C, 66·8; H, 7·4%), prepared by treating with aniline the product obtained by refluxing diethyl *n*-butylphosphonate [prepared by Ford-Moore (unpublished result) from *n*-butyl bromide *via* an Arbusov rearrangement] with thionyl chloride, had m. p. 147—148° and depressed the m. p. of the dianilides (5) and (6).

(7) and (8) The phosphonyl dichloride sublimed at the m. p. It resembled camphor in appearance and odour. The dianilides were identical (mixed m. p.).

(9) Yield calc. on cetyl chloride. The constitution as *sec.*-derivative is assumed by analogy. The dianilide, free acid, and aniline salt were all pasty solids which could not be recrystallised.

(10) Yield calc. on *cyclo*hexyl chloride. Clayton and Jensen (*J. Amer. Chem. Soc.*, 1948, **70**, 3880) give for the dichloride, b. p. 127·5—128·2°/15—16 mm. and m. p. 37—37·5°. Soborovski *et al.* (*Dokl. Akad. Nauk. U.S.S.R.*, 1949, **67**, 293) give 93—94°/1 mm. and m. p. 39—40°.

(11) Yield calc. on benzyl chloride.

(12) Procedure D led to a rise in temperature and complete solution of the aluminium chloride but no product was obtained on hydrolysis. Direct esterification of this solution also failed to give a product. The dianilide was identical with that from (18).

(13) The dianilide was identical (mixed m. p.) with that obtained by treating di*iso*propyl allylphosphonate successively with thionyl chloride and aniline. The ester was obtained from allyl bromide *via* the Arbusov rearrangement (Ford-Moore, unpublished).

(14) The reaction conditions described were the minimum which produced a reasonable yield. By A (1 week) the yield was nil, by E (24 hours) 18%, and by D (4 hours) 36%. The anilide was an amorphous solid which was purified as far as possible by rubbing it with light petroleum. The acid, produced by treatment of the dichloride with water, was hygroscopic.

(16) The aluminium chloride complex, recrystallised from methylene chloride, had m. p. 105—108°. A repetition of the preparation with 0·5 mol. of aluminium chloride gave a complex, m. p. 107° (decomp.), but differing in being much more soluble in methylene chloride. Numerous attempts to prepare a dianilide led only to trianilinophosphine oxide, m. p. 216—217°, identical with a specimen prepared from phosphorus oxychloride.

(17) The trianilide was prepared by heating the product with aniline, and the dianilide by treatment in the cold. Kabachnik *et al.* give dianilide, m. p. 169—170° (*Bull. Acad. Sci. U.R.S.S., Classe Sci. Chim.*, 1947, 97).

(20) and (21) Increased reaction time decreased the yield of dichloride. Aniline derivatives could not be made.

(22) The constitution is assumed by analogy. No material with b. p. higher than 123°/1 mm. was present.

(23) The dianilide was identical with that from (15).

(24) The anilide was identical (mixed m. p.) with that from (16).

(25) The dianilide was identical (mixed m. p.) with that from (17).

(26) The yield was good, but cannot be quoted as most of the product was lost. The product, purified by vacuum-sublimation, contained no fluorine. A crystalline aniline derivative could not be prepared.

(27) and (28) The aniline salt was identical (mixed m. p.) with that from (14).

(29) The product was identical (mixed m. p.) with that from (16).

(30) and (31) The dianilides were identical (mixed m. p.) with that from (2).

(32) When the reaction product was hydrolysed in the usual way, no product was isolated. By direct esterification of the complex a 75% yield of ethyl diethylphosphinate was obtained.

(33) Phosphorus but no chlorine was present. The product may be ethyl*iso*propylphosphinic anhydride ($C_{10}H_{24}O_3P_2$ requires C, 47·2; H, 9·45%).

(34) No product was obtained by treatment with water. By direct esterification of the complex, ethyl ethylphosphonate was obtained.

(35) The dianilide was identical (mixed m. p.) with that from (3).

(36) The dianilide was identical (mixed m. p.) with that from (7).

and the alkyl chloride run slowly into the heated mixture. Excess of phosphorus trichloride was recovered by distillation. Temperatures and period of addition were as indicated.

D. The reagents were mixed, and heated in a sealed vessel at 100° for the period indicated.

E. The reagents were mixed and heated under reflux for the period indicated.

F. Aluminium chloride was suspended in phosphorus trichloride, and the gaseous alkyl halide passed slowly through the heated mixture. Excess of phosphorus trichloride was recovered by distillation.

Isolation of Phosphonyl Chloride.—Hydrolysis of aluminium chloride complexes, except in experiment 3, was accomplished as follows. The complex was dissolved in methylene chloride (about 5—10 volumes) and the solution cooled to about −20° by the addition of solid carbon dioxide. Water was then added in small portions with vigorous shaking until the milky suspension at first formed suddenly coagulated. The quantity of water required is recorded in the Table. The solution was rapidly filtered, the solvent driven off on a water-bath, and the residue distilled or allowed to crystallise.

Characterisation of Phosphonyl Compounds.—The dichloride was warmed with an excess of aniline and the product dissolved in benzene and washed with dilute hydrochloric acid. After evaporation to dryness the residue was recrystallised, usually from aqueous alcohol, but sometimes from benzene–chloroform.

Esterification of Complexes.—The complex (*e.g.*, from experiment 2) in methylene chloride (500 ml.) was cooled with solid carbon dioxide to about −20°. Absolute ethyl alcohol was then added cautiously until the vigorous reaction had subsided. The solution was then treated with small quantities of water until the milky suspension first formed suddenly coagulated, then filtered, and the filtrate was fractionated.

The Table contains only experiments from which identifiable phosphonyl dichlorides (or corresponding derivatives) were isolated. The following are some experiments from which identified phosphonyl derivatives were not obtained.

s-*Tetrachloroethane.* Procedure D (24 hours) with equimolecular proportions was used. On hydrolysis, apart from unchanged tetrachloride, only a very small amount of a substance, b. p. 58—80°/1 mm., was obtained.

Pentachloroethane. Procedure E (4 hours) and molecular proportions C_2HCl_5 0·25, PCl_3 0·25, and $AlCl_3$ 0·5 were used. On hydrolysis and after evaporation of solvent, phosphorus oxychloride (12·5 g.), unchanged pentachloride (3·5 g.), and a substance, b. p. 83—92°/3 mm. (17 g.), were obtained. Redistillation of the last did not lead to any product of constant b. p. (Found: C, 9·6; H, 0·7; hydrolysable Cl, 25·5. Calc. for C_2HOCl_4P: C, 8·4; H, 0·35; hydrolysable Cl, 24·9%). A crystalline derivative could not be obtained.

Hexachloroethane. Procedure D (24 hours) with mol. proportions C_2Cl_6 0·25, PCl_3 0·5, and $AlCl_3$ 0·5 was used. On hydrolysis unchanged hexachloride (30 g.) and phosphorus oxychloride (30 g.) were obtained.

Tetrachloroethylene. Procedure E (24 hours) with mol. proportions C_2Cl_4 0·25, PCl_3 0·25, and $AlCl_3$ 0·5 was used. On hydrolysis only phosphorus oxychloride (20 g.) was isolated.

Chlorotrifluoromethane. Procedure F. After 6 hours no change in the appearance of the reagents had occurred and no product was isolated after hydrolysis.

Attempted Preparation of Bisphosphonyl Derivatives.—(i) 1-Chloroethylphosphonyl dichloride (0·12 mol.) was refluxed for 10 hours with phosphorus trichloride (0·25 mol.) and aluminium chloride (0·25 mol.) after which all solid had disappeared. On hydrolysis only unchanged starting material (12 g.; b. p. 57—61°/4 mm.) was obtained. (ii) Ethylene dichloride (0·5 mol.) was refluxed for 24 hours with phosphorus trichloride (1·2 mols.) and aluminium chloride (2·0 mols.), all of which went into solution. On hydrolysis no material with b. p. above 70°/3 mm. was obtained (b. p. of $C_2H_4Cl{\cdot}POCl_2$ is 77°/6 mm.).

Reaction between Ethers and Phosphorus Trichloride.—(i) Diethyl ether (0·25 mol.) was added to a mixture of phosphorus trichloride (0·5 mol.) and aluminium chloride (0·5 mol.), all reagents being first cooled to 0°. When the initial vigorous reaction had died down, the mixture was heated to 100° in a sealed tube for 7 hours; all solid had disappeared. The white crystals to which the product set on cooling were dissolved in methylene chloride and hydrolysed (6 mols. of water). After filtration and distillation, 28 g. (0·19 mol.) of ethylphosphonyl dichloride were obtained. (ii) 2 : 2′-Dichlorodiethyl ether (0·25 mol.) in a similar way gave 23 g. (0·13 mol.) of 2-chloroethylphosphonyl dichloride (Found: C, 13·6; H, 2·4. Calc. for $C_2H_4OCl_3P$: C, 13·2; H, 2·2%) together with some unchanged ether. The trianilide was identical (mixed m. p.) with that from Expt. 17. (iii) Di-*n*-butyl ether (0·25 mol.) similarly gave 34 g. (0·21 mol.) of *sec.*-butylphosphonyl dichloride, b. p. 61°/3 mm., the dianilide, m. p. 150°, being identical

with that from Expts. 5 and 6. In addition there were 20 g. of material, b. p. 62—120°/3 mm., which was not identified.

Aluminium Chloride Complex from Ethyldichlorophosphine.—Equimolecular proportions of ethyldichlorophosphine and aluminium chloride reacted vigorously to give a liquid product. Chlorine passed into this was absorbed readily. When absorption ceased all the chlorine was removed by passing carbon dioxide through the liquid. On cooling, a solid mass was obtained which crystallised from methylene chloride in cubic crystals, m. p. 199—245°. A similar substance was obtained by mixing, in equimolecular proportions, ethylphosphorus tetrachloride and aluminium chloride. The complex from Expt. 2, when recrystallised from methylene chloride formed needles, m. p. 201—235°. The two complexes when mixed had m. p. 150—210°, but moisture was probably absorbed during manipulation. The cubic crystals (28·7 g), when hydrolysed in the usual way, gave 10·5 g. (83%) of ethylphosphonyl dichloride, b. p. 40°/2 mm. (identified as the dianilide).

Action of Alkyl Chloride on the Complexes.—The complex from Expt. 2 (35 g.) was heated under reflux for 24 hours with *n*-propyl chloride. On hydrolysis, 12·5 g. (81%) of ethylphosphonyl dichloride, b. p. 40°/2 mm. (identified as dianilide), were obtained with no trace of higher-boiling material. The complex with boiling carbon tetrachloride gave 83% of ethylphosphonyl dichloride with no trace of higher-boiling material.

Action of Hydrogen Sulphide on Complexes.—(*a*) Crystalline ethyl chloride–phosphorus trichloride–aluminium chloride complex (63 g., 0·19 mol.) was loosely packed in a vertical glass tube into the bottom of which hydrogen sulphide was introduced in a slow stream, the tube being kept at 90—100°. After 200 hours no more hydrogen chloride was evolved. The liquid residue was dissolved in methylene chloride and decomposed with water (35 ml.). After filtration and removal of the solvent a solid residue of *dithiophosphoethane* (20 g., 85%) was obtained which crystallised from carbon tetrachloride in glistening plates, m. p. 157° (Found: C, 20·0; H, 4·1. $C_2H_5S_2P$ requires C, 19·4; H, 4·05%). When this was warmed with water some went into solution with evolution of hydrogen sulphide. The residue on recrystallisation from light petroleum had m. p. 54—55° and was identified as *thiophosphoethane* (Found: C, 22·4; H, 4·9; S, 30·0. C_2H_5OSP requires C, 22·2; H, 4·7; S, 29·7%). The solution on evaporation gave a small quantity of hygroscopic solid, which after drying (P_2O_5) had m. p. 55—56° [the m. p. of ethylphosphoric acid is given by Kosolapoff (*J. Amer. Chem. Soc.*, 1945, **67**, 1180) as 61—62°]. Thiophosphoethane did not appear to be appreciably decomposed by prolonged boiling in water.

(*b*) The crystalline complex (75 g., 0·22 mol.) was treated for 7 hours with hydrogen sulphide. The partly liquid product when hydrolysed (50 ml. water) in the usual way yielded thiophosphoethane (11·5 g., 47%) and ethylthiophosphonyl dichloride (13 g., 32%) (Found: C, 14·7; H, 3·1; Cl by hydrolysis, 44·2. Calc. for $C_2H_5Cl_2SP$: C, 14·7; H, 3·0; Cl, 43·5%), b. p. 54°/4 mm. Guichard (*Ber.*, 1899, **32**, 1572) gives b. p. 80—82°/50 mm. The *dianilide* had m. p. 112—114° (Found: C, 59·1; H, 6·4. $C_{14}H_{17}N_2SP$ requires C, 60·9; H, 6·2%). Ford-Moore (unpublished) gave the m. p. of the dianilide obtained from the dichloride, prepared by a modification of Guichard's method, as 114°. Repetitions of this experiment with variations in temperature and time of passage invariably yielded a mixture of thio- and dithio-phosphoethane and the dichloride, with the last as the minor constituent.

(*c*) The crystalline complex (90 g., 0·27 mol.) was treated with hydrogen sulphide at 130° until reaction had ceased. The residue was dissolved in methylene chloride. One half of this solution, on decomposition with concentrated hydrochloric acid, filtration, and evaporation, gave a residue of practically pure dithiophosphoethane (14·5 g., 63%). The other half was shaken with 50 ml. of ethyl alcohol, and the solvent and excess of alcohol were distilled off. The residue was dissolved in methylene chloride, decomposed with water, filtered, and distilled. O-*Ethyl hydrogen ethyldithiophosphonate*, b. p. 85°/1 mm. (12·6 g., 40%), was thus obtained (Found: C, 27·8; H, 6·6. $C_4H_{11}OS_2P$ requires C, 28·2; H, 6·5%).

(*d*) The crystalline methyl chloride complex (71 g., 0·22 mol.) was treated at 130° with a stream of hydrogen sulphide until after 100 hours no more hydrogen chloride was evolved. The residue, which solidified on cooling, was dissolved in methylene chloride and decomposed with water (40 ml.). On evaporation a solid residue was obtained, having m. p. 197—200°, not improved after sublimation *in vacuo*. This proved to be *thiophosphomethane* (20 g., 98%) (Found: C, 12·8; H, 3·2. CH_3OSP requires C, 12·8; H, 3·2%).

Electrolysis of Ethyl Chloride–Phosphorus Trichloride–Aluminium Chloride Complex.—(i) The complex was dissolved in methylene chloride and a current passed through it. Aluminium chloride was precipitated at the anode. The liquid at the cathode smelled strongly of phos-

phines, but only a very small quantity of a substance, b. p. 35—85°/5 mm., which, by the formation of the dianilide, was shown to contain ethylphosphonyl dichloride, could be isolated. (ii) The complex (100 g., 0·29 mol.) was dissolved in methylene dichloride (200 ml.) and placed in an apparatus consisting of a porous pot fitted with a reflux condenser and a silver cathode dipping into a glass vessel with reflux condenser and platinum anode. The apparatus was cooled in solid carbon dioxide. The electrodes were connected across the 220-v DC mains. Current flowed at 1·15 amp., falling slowly to 0·5 amp. after 5 hours and to 0·2 amp. after a further hour. Whilst electrolysis proceeded a slow stream of chlorine was passed into the cathode compartment. Anhydrous aluminium chloride (20·7 g., 55%) was recovered from the anode compartment. From the cathode were obtained 50 g. of a white solid with an odour resembling that of camphor (Found : hydrolysable Cl, 49·3%). It reacted readily with sulphur dioxide to give a liquid from which thionyl chloride was recovered, together with a high-boiling material which solidified on cooling. The latter had an indefinite m. p., contained inorganic matter, and was not identified.

Microanalyses were carried out by Mr. F. E. Charlton, to whom the authors express their gratitude. They are grateful to the Chief Scientist, Ministry of Supply, for allowing them freedom from other duties during 1948 to undertake this research. Acknowledgment is also made to him for permission to publish.

EXPERIMENTAL ESTABLISHMENT, PORTON,
NEAR SALISBURY, WILTS.

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662. *The* Senecio *Alkaloids. Part IX.* The Synthesis and Resolution of* 3 : 4-*Dihydroxy*-2-*methylpentane*-3-*carboxylic Acids: Viridifloric and Trachelantic Acids.*

By LEONARD J. DRY and FRANK L. WARREN.

4-Methylpent-2-ene-3-carboxylic acid (I) is oxidised by perbenzoic acid and the product hydrolysed to (±)-*erythro*-3 : 4-dihydroxy-2-methylpentane-3-carboxylic acid (IV), m. p. 148—150°. This is resolved into its optical components which shows no measurable rotation. The acid (I) is also oxidised by dilute potassium permanganate, giving (±)-*threo*-3 : 4-dihydroxy-2-methylpentane-3-carboxylic acid (II), m. p. 119—121°, which is resolved into the (+)-form, $[\alpha]_D^{20}$ +2·2°, and the less pure (−)-form, $[\alpha]_D^{20}$ −1°.

The significance of these results is discussed in relation to the configurational relations of trachelantic and viridifloric acids.

TRACHELANTIC ACID, m. p. 93—95°, has been obtained by the alkaline hydrolysis of trachelantine (Menshikov, *J. Gen. Chem., U.S.S.R.*, 1941, **11**, 209; cf. also Menshikov and Borodina, *ibid.*, 1945, **15**, 225), lindifoline (Menshikov, *ibid.*, 1948, **18**, 1836), and supinine (Menshikov and Gurevich, *ibid.*, 1949, **19**, 1382). Menshikov (*ibid.*, 1947, **17**, 343) reported the acid as inactive and showed it to be 3 : 4-dihydroxy-2-methylpentane-3-carboxylic acid. The same author (*loc. cit.*, 1949) was able to isolate (+)-trachelantic acid, m. p. 93—94°, $[\alpha]_D$ +1·3° (in water), by catalytic hydrogenolysis of supinine. An isomeric acid, viridifloric acid, m. p. 119—121°, was obtained by the hydrolysis of viridiflorine (Menshikov, *ibid.*, 1948, **18**, 1736).

Adams and Herz (*J. Amer. Chem. Soc.*, 1950, **72**, 155) synthesised one form of (±)-3 : 4-dihydroxy-2-methylpentane-3-carboxylic acid (II), m. p. 119°, by the oxidation of 4-methylpent-2-ene-3-carboxylic acid (I) with dilute potassium permanganate. They naturally concluded that their synthetic acid (II) was identical with viridifloric acid which Menshikov had reported was optically inactive. They indicated that they were unable to obtain the other form of the dihydroxy-acid, and were not prepared to assign a configuration to their synthetic acid. It would seem, however, from Braun's studies (*ibid.*, 1929, **51**, 228) that the acid (II) was the *threo*-form.†

* Part VIII, *J.*, 1951, 66.

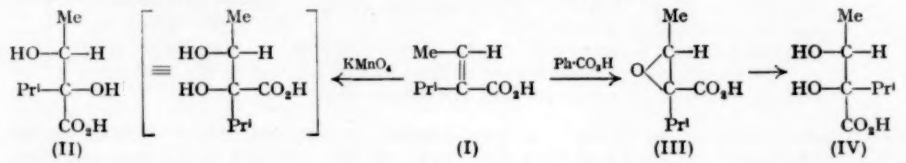
† Throughout this paper the stereochemical designations refer to the four-carbon chain shown vertically in the formulæ. The formulæ refer to the form shown, its mirror image, or the optically inactive form, as the case may require.

The other modification of this dihydroxy-acid has now been synthesised. The unsaturated acid (I) was converted by perbenzoic acid into the epoxide (III), which was not isolated but was hydrolysed to give, by *trans*-addition, (±)-*erythro*-3 : 4-dihydroxy-2-methylpentane-3-carboxylic acid (IV), m. p. 148—150°. This acid was certainly not identical with natural trachelantic acid. The validity of the structure followed not only from the synthesis. The synthetic acid showed the characteristics of an α-hydroxy-acid, and oxidation with lead tetra-acetate gave acetaldehyde, identified and estimated as the dimedone derivative, m. p. 138°, and its anhydro-form, m. p. 174°, in 68% yield.

Menshikov's trachelantic acid could be the (+)-form of this *erythro*-acid (IV). Accordingly the brucine salt of the pure (±)-acid (IV) was crystallised from absolute alcohol; the less soluble salt, m. p. 184—186°, yielded an acid (IV*a*), m. p. 117—119°. The more soluble brucine salts, recovered from the alcoholic solution by evaporation, were extracted many times with acetone, to leave a salt, m. p. 207—210°, which gave the enantiomorphous acid (IV*b*), m. p. 114—115°.

The brucine salts remaining in the acetone were recrystallised from this solvent, to give a less pure brucine salt, which yielded an acid, m. p. 120—130°, showing after sublimation, m. p. 118—122°. The melting points of both optical forms (IV*a*) and (IV*b*) were depressed about 30° on admixture with the (±)-*threo*-form (II). Neither of the enantiomorphs showed measurable rotation; but a mixture of the two showed a melting-point elevation to 140—143°. Addition of the (±)-modification (IV) to either of its optical components always showed a melting-point rise, the amount of which increased with increasing amounts of the (±)-form. This observation implied that the racemic form (IV) formed solid solutions with its enantiomorphs so that trachelantic acid could be neither a pure, nor a partly racemised, enantiomorph of the *erythro*-acid (IV).

Reinvestigation of Adams and Herz's synthesis (*loc. cit.*) confirmed the formation of an acid, m. p. 119—121°, which is formulated as (±)-*threo*-3 : 4-dihydroxy-2-methylpentane-3-carboxylic acid (II). Resolution of this acid through the brucine salt gave the (+)-acid (II*a*), m. p. 92°, and a slightly optically impure (−)-acid (II*b*), m. p. 84°. A mixture of the (+)- and the (−)-acid showed m. p. 114—118°. The melting points of both (II*a*) and (II*b*) were depressed on admixture with a small amount of (II).



(II), m. p. 119—121°
(II*a*), m. p. 92°, [α]$_D$ +2·2°
(II*b*), m. p. 83—85°, [α]$_D$ −1°
(II*a* + *b*), m. p. 114—118°

(IV), m. p. 148—150°
(IV*a*), m. p. 117—119°, [α]$_D$ ± 0°
(IV*b*), m. p. 118—122°, [α]$_D$ ±0°
(IV*a* + *b*), m. p. 140—143°

In the absence of an authentic specimen the identification of viridifloric acid with Adams and Herz's synthetic acid (II) (*loc. cit.*) is not completely satisfactory. Viridifloric acid could be either one of the *erythro*-acids (IV*a* or *b*). It seems, however, in the light of our findings tabulated above, that trachelantic acid, m. p. 93—95°, is (+)-*threo*-3 : 4-dihydroxy-2-methylpentane-3-carboxylic acid (II*a*).

It follows from configurational studies on αβ-unsaturated acids by Auwers and Weissbach (*Ber.*, 1923, **56**, 715; cf. also Auwers *et al.*, *Annalen*, 1923, **432**, 46) that our unsaturated acid (I) is almost certainly the stable *cis*-modification with respect to the carbon chain (cf. tiglic acid, Titov, *J. Gen. Chem., U.S.S.R.*, 1948, **18**, 1467). The configuration of the two acids, *threo* (II) and *erythro* (IV), follows from the *cis*- and *trans*-addition respectively of the hydroxyl groups across the double bond. These findings parallel those of the oxidation by potassium permanganate (*i.e.*, *cis*-addition) of the geometrical isomers of both but-2-ene-2-carboxylic acid (Fittig and Penschuck, *Annalen*, 1894, **283**, 109, 114) and pent-2-ene-3-carboxylic acid (Fittig, *ibid.*, 1892, **268**, 22) : the stable forms of these

acids give the lower-melting dihydroxy-acids whilst the labile forms yield the dihydroxy-acids with the higher melting point.

The preparation of acid (I) was essentially that used by Adams and Herz (*loc. cit.*). The yield, however, of the mixed unsaturated esters formed from the dehydration of ethyl 4-hydroxy-2-methylpentane-3-carboxylate is now raised to over 80% whilst the time required for the operation is decreased to less than an hour and charring is nearly completely avoided by a simple modification of Kon and Nargund's method (*J.*, 1932, 2461). Furthermore, an ultra-violet extinction curve showed that the mixed unsaturated acids ($\lambda_{max.}$ 213; $\varepsilon_{max.}$ 5100 in alcohol) contained only about 60% of the pure αβ-unsaturated acid ($\lambda_{max.}$ 213; ε 8600) at equilibrium. The method of separation of the required αβ-unsaturated acid (I) by partial esterification (cf. Eccott and Linstead, *J.*, 1929, 2160) did not readily give a separation. The αβ-acid was readily separated by initially freezing out and then removing the liquid βγ-form by differential extraction with a calculated quantity of sodium hydrogen carbonate. The derived mixture of αβ- and βγ-unsaturated acids was then heated with potassium hydroxide solution, and the αβ-unsaturated acid separated as above. This process was repeated twice.

Experimental

Analyses are by Drs. Weiler and Strauss, Oxford, and spectroscopic data by M. E. von Klemperer of these laboratories. M. p.s are uncorrected.

Dehydration of Ethyl 4-Hydroxy-2-methylpentane-3-carboxylate.—The ester (143 g., 0·82 mol.) in pure dry benzene (200 ml.) was heated to boiling and vigorously stirred whilst phosphoric oxide (118 g., 0·83 mol.), mixed to a paste with benzene (150 ml.), was added during 30 minutes. The mixture was refluxed for a further 20 minutes and cooled. The supernatant liquid was poured off and the metaphosphoric acid residue washed with benzene. The combined solution and washings gave a mixture of unsaturated esters (70 g.), b. p. 75—80°/22 mm. The phosphoric acid residues were taken up with hot water, and the solution was extracted with benzene which, after being washed and dried, gave a further quantity of ester (34 g.). The total yield was 81%.

4-Methylpent-2-ene-3-carboxylic Acid (I).—The mixture of unsaturated esters (104 g.) was heated under reflux for 45 minutes with potassium hydroxide (93 g.) in 85% ethanol (500 ml.). The solvent was removed under reduced pressure and the residue acidified with dilute sulphuric acid, an oily layer, which partly solidified on chilling, then separating. The αβ-unsaturated acid was filtered off and the residual acid layer was taken up in ether. The ethereal solution was re-extracted with a calculated volume of a solution of sodium hydrogen carbonate to remove two-thirds of the total remaining acids. The remaining ethereal layer contained a further quantity of predominantly αβ-unsaturated acid which, combined with the first batch, crystallised from 25% ethanol, to give 4-methylpent-2-ene-3-carboxylic acid (31 g.), m. p. 54° (Found: C, 65·6; H, 9·6. Calc. for $C_7H_{12}O_2$: C, 65·6; H, 9·4%).

The liquid acid mixture (1 mol.) obtained from the sodium hydrogen carbonate extract was heated for 16 hours at 97° with 20% alcoholic potassium hydroxide (10 mols.). The acidified solution was worked up as above to give a further quantity of pure αβ-unsaturated acid (15 g.). By repeating this equilibration it was possible to isolate a total of 60 g. of pure acid.

(±)-erythro-3 : 4-*Dihydroxy-2-methylpentane-3-carboxylic Acid.*—4-Methylpent-2-ene-3-carboxylic acid (25 g., 1 mol.) was dissolved in 0·92N-perbenzoic acid in dry chloroform (1·1 mols.). After 22 days at 8° the oxidation was practically complete, whereupon water (200 ml.) and 2N-sulphuric acid (20 ml.) was added. The chloroform was partly removed by evaporation, and the residual mixture refluxed for 3 hours. The aqueous layer was separated, washed twice with benzene to remove benzoic acid and a little unchanged unsaturated acid, neutralised with sodium carbonate, and evaporated under reduced pressure. The concentrate, acidified with concentrated hydrochloric acid, was extracted with ether. The ethereal solution, washed twice with a little saturated sodium chloride solution and dried (Na_2SO_4), gave a crude acid (9·2 g.). This acid was boiled out with benzene, and the insoluble material (7·2 g.) crystallised from ether–light petroleum in granules. Sublimation at 93—94°/6 μ gave (±)-erythro-3 : 4-*dihydroxy-2-methylpentane-3-carboxylic acid*, m. p. 148—150° (Found: C, 51·8; H, 8·7. $C_7H_{14}O_4$ requires C, 51·8; H, 8·7%). The p-*phenylphenacyl* ester crystallised from dilute ethanol and then from benzene–light petroleum in small stout prisms, m. p. 123—124° (Found: C, 70·35; H, 6·75. $C_{21}H_{24}O_5$ requires C, 70·75; H, 6·8%).

(±)-threo-3 : 4-*Dihydroxy-2-methylpentane-3-carboxylic Acid.*—4-Methylpent-2-ene-3-carboxylic acid (12·8 g.) was oxidised by potassium permanganate as described by Adams and Herz

(*loc. cit.*), to yield crude (±)-*threo*-acid (5·8 g.) whilst some unsaturated acid (2·7 g.) was recovered. The crude acid solidified when stirred with light petroleum and crystallised from ethyl acetate–light petroleum or chloroform–light petroleum, giving the (±)-*threo*-acid, m. p. 116—119°. When sublimed at 80°/0·2 mm., it had m. p. 119—121°. Adams and Herz (*loc. cit.*) give m. p. 119°. The p-*phenylphenacyl* ester crystallised from benzene–light petroleum in needles, m. p. 96—97° (Found, after drying at 72°/0·2 mm.: C, 71·0; H, 6·9%).

Resolution of (±)-threo-*Acid*.—The brucine salt from recrystallised acid (6·9 g.) in absolute ethanol (160 ml.) was kept for 12 hours at room temperature and finally cooled to 8°. The crystalline salt (11 g.) was recrystallised four times from ethanol, to give the *brucine* (+)-*acid* salt (7 g.), m. p. 225° (Found: C, 64·4; H, 7·3. $C_{30}H_{40}O_8N_2$ requires C, 64·7; H, 7·2%). The regenerated acid, crystallised from chloroform–light petroleum, gave the (+)-*acid*, m. p. 89—90°, $[\alpha]_D^{20}$ +2·2°±0·2° (*c*, 1 in ethanol), $[\alpha]_D^{20}$ +2°±0·5° (*c*, 1 in water) (Found: C, 51·8; H, 8·5%). Sublimation at 60°/0·2 mm. gave the (+)-acid, m. p. 92° (Found: C, 51·7; H, 8·5%). The unsublimed acid slowly became sticky but the sublimed acid was stable. A solution of the soluble brucine salt, concentrated to 100 ml. and cooled to 0° for 48 hours, gave crystals, m. p. 196—198°. The regenerated (−)-acid, crystallised from chloroform–light petroleum, had m. p. 70—75°, $[\alpha]_D^{20}$ −0·75° (*c*, 1 in water). Sublimation at 58°/0·2 mm. gave the (−)-*acid*, m. p. 83—85° (Found: C, 52·4; H, 8·9%).

Resolution of (±)-erythro-*Acid*.—The brucine salt (26 g.) was crystallised four times from absolute ethanol, to yield a *salt*, m. p. 184—186° (Found: C, 65·2; H, 7·2%). This yielded an acid, which, twice sublimed, gave the erythro-*acid* (IV*a*), m. p. 117—119°, $[\alpha]_D$ ±0° (*c*, 1 in water) (Found: C, 51·65; H, 8·5%). The remaining brucine salts (B) were extracted with boiling acetone (100 ml.) for 20 minutes and the solution filtered hot. This process was repeated ten times with decreasing volumes of acetone, the final volume being 8 ml., to leave a salt, m. p. 207—210° (Found: C, 64·9; H, 7·2%). This yielded an acid which, crystallised from ethyl acetate–light petroleum, gave the erythro-*acid* (IV*b*), m. p. 114—115°, $[\alpha]_D$ ±0° (*c*, 1 in water) (Found: C, 51·5; H, 8·55%). On another occasion, the brucine salts (B) were crystallised from acetone three times and the derived salt, m. p. 195—200°, gave an acid, m. p. *ca.* 120—130°, which on sublimation gave m. p. 119—122°.

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University of Natal, Pietermaritzburg, South Africa. [*Received, May 5th,* 1952]

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663. *New Syntheses based on 5-Aminopyrimidines.*

By F. L. Rose.

A series of 5-aminopyrimidines (most of them substituted in position 2 by additional amine residues) has been prepared, and the similarity of the behaviour of the 5-amino-group to that in aromatic primary amines has been demonstrated. The 5-amino-group can be diazotised, but the presence of a 4(6)-mercapto-, -hydroxyl, or primary -amino-group leads to rapid formation, even under acid conditions, of pyrimidino-thiadiazoles, -oxadiazoles, and -triazoles, respectively. Ring-closure also occurs, most readily in the presence of caustic alkali, when alkyl groups are present in positions 4 and 6. The products are 1 : 2 : 4 : 6-tetra-azaindenes, isomeric with the purines, and one such compound, 5-amino-7-methyl-1 : 2 : 4 : 6-tetra-azaindene exhibits anti-tuberculous activity *in vivo*. The preparation of many homologues and analogues is described. The 5-amino-group exhibited normal behaviour towards acylating agents and in its reaction with dicyanimide and dicyandiamides from which a series of pyrimidyldiguanides was prepared.

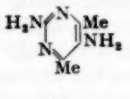
Many 5-aminopyrimidines have been prepared in the course of numerous researches in the purine and pteridine fields, but comparatively little work has been undertaken on the behaviour of these substances towards diazotisation, a property which they theoretically possess in common with 3-aminopyridines. Boarland and McOmie (*J.*, 1951, 1218) commented on the failure of 5-aminopyrimidine itself to give a diazonium compound when

treated with nitrous acid, but it has been found in these laboratories that the introduction of certain substituents into the pyrimidine ring leads to amines often capable of forming very stable diazonium salts. Initial attention was drawn to this influence when the properties of 2 : 5-diamino-4 : 6-dimethylpyrimidine (I), prepared by Todd and his co-workers for use in drug syntheses (*J.*, 1946, 357; 1947, 41), were studied in detail. When this substance was treated with nitrous acid at 20°, the 2-amino-group was unchanged, but the 5-amino-group was converted into a diazonium group, which only slowly decomposed, even when the solution was warmed.

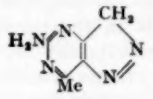
A potential chemotherapeutic interest in this particular diazonium compound arose from the observation that the methyl groups were so activated (additively by the ring-nitrogen atoms and the diazonium group) that a form of internal coupling occurred under certain conditions to give (II) or (III) in a manner analogous to the production of indazoles from *o*-toluidines. The bicyclic system so formed was isomeric with that of the purine (IV), the 8 : 9-components of the glyoxaline ring of the latter having been transposed to yield the pyrazole analogue. Despite this re-arrangement, the new compound was physically and chemically very similar to the true purine in that it was amphoteric, exhibited marked fluorescence in solution at high dilution, and possessed very similar ultra-violet absorption.

Functional derivatives of various condensed pyrimidine systems have been studied during the last few years by several groups of workers, particularly as "purine antagonists." As a consequence, the triazolopyrimidine (V) (Roblin, Lampen, English, Cole, and Vaughan, *J. Amer. Chem. Soc.*, 1945, **67**, 290) and 2 : 6-diaminopurine have proved of experimental interest in the treatment of leukæmia. Dr. Walpole, in these laboratories, examined several compounds of type (III) against mouse leukæmia, including (XIII; $R^1 = NH_2$, $R^2 = OH$, $R^3 = H$) and the diamine (VI), analogous to the substances referred to, but was only able to detect marginal activity. On the other hand, (III) was found by Mr. J. Francis and Dr. A. R. Martin to exhibit marked action against tubercular infections in mice (method of Martin, *J. Path. Bact.*, 1946, **58**, 580). These results will be reported elsewhere in detail, but they clearly called for a thorough chemical investigation of the purine isomers, during which much new information on the properties of diazotisable aminopyrimidines came to light and is here recorded.

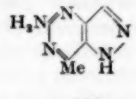
Only one example of a compound of type (III) appeared to be known. This arose from a study by Behrend (*Annalen*, 1888, **245**, 213) of the action of nitrous acid on 5-amino-6-methyluracil (VII), during which a compound was isolated that analysed as, and was given the structure (VIII). In support of this formulation it was pointed out



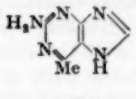
(I)



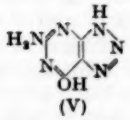
(II)



(III)



(IV)



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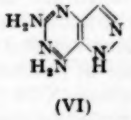

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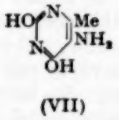
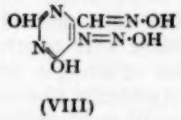
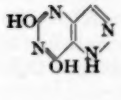


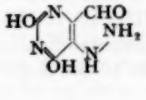
(VII)



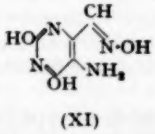
(VIII)



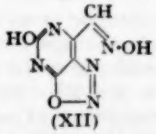
(IX)



(X)



(XI)



(XII)

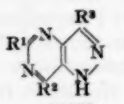
that reduction with stannous chloride gave (IX), with either the hydrazine (X) or the amino-oxime (XI) as the intermediate substance. Re-investigation of Behrend's work showed (VIII) to be a very stable compound, and moreover to be a hydrate from which water was removed in boiling dichlorobenzene but not in vacuum at 100°. The hydrate could be re-formed by crystallisation from water. The oxadiazole structure (XII) seemed

therefore more probable, and this type of substance is now known to be readily formed from 5-amino-6-hydroxypyrimidines. (It is not proposed to become involved here in the controversies about the precise structure of the oxides.) Behrend referred to (IX) as "iso-xanthine" but the use of the prefix in this connection is obviously undesirable and in the present communication this class of compound has been considered as derived from 1 : 2 : 4 : 6-tetra-azaindene. The first variations on the structure of (III) concerned the introduction of other substituents into positions 3, 5, and 7. Most of the preparations (XIII) had R^1 = basic group, but a few examples were made having hydrogen or methylthio in this position. As would be expected, the nature of the substituent R^2 in the parent diamine (XIV) markedly influenced the ease of formation of the pyrazole ring. With amino, alkylamino, hydroxy, or mercapto in this position the diazonium salt cyclised preferentially with these substituents, giving triazole, oxadiazole and thiadiazole rings respectively. Compounds of type (XIII) were successfully prepared directly from the diazotised (XIV), however, when R^2 was (in addition to alkyl) phenyl, dialkylamino, alkylthio, and carboxymethylthio. Conditions for optimum yield of the pyrazole derivatives were also dependent on the chemical characteristics of R^2. With the 4 : 6-dimethylpyrimidine (I) it was necessary to add the solution of the diazonium salt through a capillary tube below the surface of a rapidly stirred aqueous solution of an excess of sodium hydroxide. A less drastic basification, either by the slow addition of sodium hydroxide to the diazo-solution or the use of sodium carbonate or ammonia, always led to the formation of the azo-compound analysing as, and believed to be (XV). A similar behaviour was observed with (XIV; $R^1 = NH_2$, R^2 = Ph, R^3 = Me). Ring-closure using caustic alkali was also successful with (XIV; R^2 = dialkylamino) but compounds of this type were found to give even better yields when the acid solutions of the corresponding diazonium salts were kept for some time at laboratory temperature. Compound (XIV; $R^1 = NH_2$, R^2 = SMe, R^3 = Me) was also convertible into the tetra-azaindene in this manner, but in this instance only in low yield. Under such conditions the respective diazonium groups exhibited remarkable stability in that, unlike those derived from the 4 : 6-dialkylpyrimidines of type (I), there was little or no evolution of nitrogen. The rate at which ring-closure proceeded could be markedly increased by heat, again without noticeable decomposition, and indeed an almost quantitative yield of the tetra-azaindene (XIII; $R^1 = NH_2$, $R^2 = NMe_2$, R^3 = H) resulted simply when the acid solution of the parent diazonium compound was brought rapidly to the boil. In these reactions the presence of residual unchanged diazonium groups was detected by adding a drop of the solution to *m*-phenylenediamine or alkaline R-salt solution, characteristic soluble azo-coupling products being formed. The greater stability of the diazonium groups in the tertiary amino- and alkylthio-compounds, and the increased reactivity of the adjacent methyl group, could both be explained on the basis of the additional positive charge resulting from the assumed intermediate formation of the diazosulphonium and triazolinium ionic structures, (XVI) and (XVII) respectively. A salt of the former was isolated and analysed. By contrast, the diazonium salts derived from the corresponding 5-amino-4-methoxy- and -4-chloropyrimidines were relatively unstable. The solutions coupled with alkaline R-salt, but evolution of nitrogen occurred even in the presence of hydrochloric acid, and was very rapid on addition to caustic alkali. No tetra-azaindene (XIII; $R^1 = NH_2$, R^2 = OMe or Cl, R^3 = H) was isolated. A similar result was obtained on starting with 2 : 5-diamino-4-methylpyrimidine in an attempt to prepare (XIII; $R^1 = NH_2$, $R^2 = R^3$ = H), although chromatographic analysis of the final reaction mixture indicated the presence of a trace of a product similar in speed of travel and fluorescence to the methyl homologue (XIII; $R^1 = NH_2$, R^2 = Me, R^3 = H).

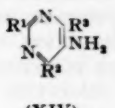
The preparation of compounds of type [XIII; R^2 = OH, NH_2, NHAlkyl, $N(Alkyl)_2$] was possible, by indirect means, by making use of the labile nature of the alkylthio-group in the tetra-azaindenes just discussed (XIII; R^2 = SAlkyl). A hydroxy-derivative (XIII; $R^1 = NH_2$, R^2 = OH, R^3 = H) resulted from oxidation of the corresponding methylthio-compound in hot glacial acetic acid with perhydrol, the methanesulphonate crystallising. Amine residues such as *iso*propylamino, piperidino, and morpholino, were introduced into the same position by heating the methylthio-tetra-azaindene with the

appropriate amine, usually under pressure at temperatures up to 150°. The diamine (VI) already referred to, was obtained in this way with ammonia.

Diazotisation and ring-closure of 4 : 6-dialkyl-5-aminopyrimidines in which the alkyl groups were different would clearly lead to mixture of two possible isomers. This has proved to be the case in the several examples examined. Thus (XIV; $R^1 = NH_2$, $R^2 = Me$, $R^3 = Et$) yielded (XIII; $R^1 = NH_2$, $R^2 = R^3 = Me$) and (XIII; $R^1 = NH_2$, $R^2 = Et$, $R^3 = H$). Separation of the isomers depended on the marked difference in the



(XIII)



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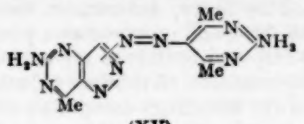
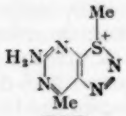
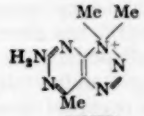


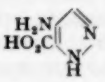
(XV)



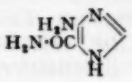
(XVI)



(XVII)



(XVIII)



(XIX)

solubilities of the hydrochlorides, and structures were assigned on the basis of comparison of the ultra-violet absorption spectra with those of (III) and (XIII; $R^1 = NH_2$, $R^2 = Et$, $R^3 = Me$), the latter being the sole possible product from the diazotisation of (XIV; $R^1 = NH_2$, $R^2 = R^3 = Et$) and regarded as typical of those tetra-azaindenes carrying an alkyl group (R^3) on the pyrazole ring. The relevant maxima and minima of ultra-violet absorption in 0·1N-sodium hydroxide are given in Table 1.

TABLE 1. *Positions of maxima and minima in the ultra-violet absorption spectra of certain tetra-azaindenes (solvent, N-sodium hydroxide).*

	Maxima (mμ)			Minima (mμ)	
(III)	231	284	343	258	309
(XIII; $R^1 = NH_2$, $R^2 = Et$, $R^3 = Me$)	236	289	358	262	314
(XIII; $R^1 = NH_2$, $R^2 = Et$, $R^3 = H$), m. p. 278—280°	228	284	338	257	311
(XIII; $R^1 = NH_2$, $R^2 = Me$, $R^3 = Me$), m. p. 327°	236	289	353	263	315
(IV)	224	268 •	301	242	345

• Point of inflexion.

The tetra-azaindene (XIII; $R^1 = NH_2$, $R^2 = Ph$, $R^3 = H$), obtained in good yield from the corresponding 2 : 5-diaminopyrimidine, was unusual in that, unlike the analogous alkyl compounds, it was markedly soluble in water as the free base, the solution again exhibiting intense fluorescence.

Some indication of the variety of substituents introduced into the 2-position of the pyrimidine ring has already been given (position R^1 in XIII). In greater detail these have included amino (already discussed), methylthio, methylamino, dimethylamino, ethylamino, *n*-propylamino, *iso*propylamino, *n*-butylamino, *iso*butylamino, *n*-amylamino, piperidino, guanidino, *p*-chlorophenylguanidino, and *p*-anisidino. In some instances, yields of the tetra-azaindenes were low. Special mention is necessary for compounds of type (XIII; $R^1 = H$). These were of particular interest in that with $R^2 = OH$ or NH_2, the products would be isomeric with hypoxanthine and adenine, respectively. So far, only the related (XIII; $R^1 = H$, $R^2 = NMe_2$, $R^3 = H$) has been prepared. Because of difficulties associated with the preparation of the parent 5-aminopyrimidine, the hydrogen was introduced into position R^1 in the ultimate reaction of the series by using the general method first employed by Mozingo, specifically, by heating the 2-methylthio-compound (XIII; $R^1 = SMe$, $R^2 = NMe_2$, $R^3 = H$) with excess of Raney nickel, containing much occluded hydrogen, in boiling dimethylformamide. The intermediate methylthio-derivative was itself prepared in very good yield by heating the acid solution of the diazonium salt from (XIV; $R^1 = SMe$, $R^2 = NMe_2$, $R^3 = Me$) at 90° for a few minutes.

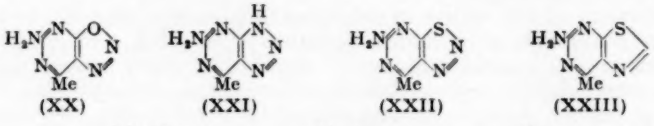
Attempts to replace the dimethylamino-group of (XIII; $R^1 = R^3 = H$, $R^2 = NMe_2$) by hydroxyl have failed. The only product of low solubility obtained by refluxing this

product with concentrated hydrochloric acid for some hours, was a diazotisable amino-acid which gave analyses for $C_4H_5O_2N_3$. This compound may be the aminopyrazolecarboxylic acid (XVIII) which might be expected to result from breakdown of the pyrimidine portion of the molecule. No rigid proof has, however, been sought. If the constitution adduced is correct, then this amino-acid is related structurally to 4-aminoglyoxaline-5-carboxyamide (XIX) formed by bacteria during sulphonamide bacteriostasis; this was initially isolated by Stetten and Fox (*J. Biol. Chem.*, 1945, **161**, 333), later shown to be constituted as formulated by Shive, Ackermann, Gordon, Getzendaner, and Eakin (*J. Amer. Chem. Soc.*, 1947, **69**, 725), and proposed as a possible precursor in purine biosynthesis. Because of this, (XVIII) was examined for antibacterial action, but was found to be devoid of activity. By contrast, (III) when refluxed with concentrated hydrochloric acid gave a good yield of the 5-hydroxy-compound (XIII; $R^1 = OH$, $R^2 = Me$, $R^3 = H$).

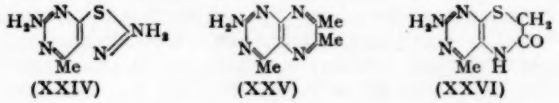
The therapeutic effect of (III) against tubercular infections led to the synthesis of a number of analogues containing a fused pyrimidine ring substituted by amino and methyl in the same manner. The corresponding purine (IV) has already been described by Gabriel and Colman (*Ber.*, 1901, **34**, 1249). The three compounds, (XX), (XXI), and (XXII), were prepared by diazotisation of the corresponding 5-amino-6-hydroxy-, 5 : 6-diamino-, and 5-amino-6-mercapto-pyrimidines. Ring-closure occurred spontaneously in the second and third instances when the acid diazonium solutions were kept for a few hours. In the case of (XX), the solution was made alkaline with ammonia, whereupon the oxadiazolopyrimidine crystallised.

Cook, Heilbron, and their co-workers (*J.*, 1949, 1064, 1069, 1071) have prepared a number of thiazolopyrimidines through ring-closure of thioureidothiazoles, and Falco and Hitchings (*J. Amer. Chem. Soc.*, 1950, **72**, 3203) have made similar compounds as functional derivatives of condensed pyrimidine systems and therefore potential antimicrobial agents. The two compounds (XXIII) and (XXIV), however, appear to be new. The former was synthesised when (XIV; $R^1 = NH_2$, $R^2 = Me$, $R^3 = SH$) was refluxed with formic acid, while the latter was obtained initially as the hydrochloride when a solution of (XIV; $R^1 = NH_2$, $R^2 = Me$, $R^3 = Cl$) in dilute hydrochloric acid was refluxed with potassium thiocyanate. The pteridine (XXV) resulted from the direct action of diacetyl on (XIV; $R^1 = R^3 = NH_2$, $R^2 = Me$) in aqueous solution at 80°, whereas the dihydroketothiazine (XXVI) was formed when the corresponding thioglycollic acid (XIV; $R^1 = NH_2$, $R^2 = Me$, $R^3 = S{\cdot}CH_2{\cdot}CO_2H$) was heated in dilute hydrochloric acid solution. Not one of these analogues of (III) exhibited therapeutic activity.

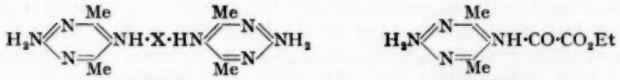
The availability of the many 5-aminopyrimidines prepared in the course of this research prompted a study of the properties, other than diazotisation followed by ring-closure, conferred by the amino-group in this position. The several reactions studied centred



(XX) (XXI) (XXII) (XXIII)



(XXIV) (XXV) (XXVI)



(XVII) (XXVIII)

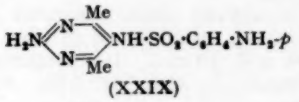
mainly round the simple diamine (I). This substance is itself unusual. Not only is it freely soluble in cold water (>20%), but the solutions exhibit a strong fluorescence even at high dilution. The monohydrochloride is less soluble than the base and does not fluoresce. Acetylation and benzoylation gave the 5-acyl derivatives, since the products

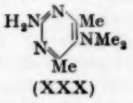
did not react with nitrous acid. Treatment with carbonyl chloride in aqueous solution in the presence of sodium acetate readily yielded the symmetrical urea (XXVII; X = CO), and treatment with ethyl malonate alone at 200° gave the malondiamide (XXVII; X = $CO{\cdot}CH_2{\cdot}CO$). Ethyl oxalate under reflux gave mainly the oxamic ester (XXVIII). The sulphanilamide derivative (XXIX) of (I) was prepared by the action on the latter of *p*-nitrobenzenesulphonyl chloride in the presence of aqueous sodium acetate, followed by reduction of the nitro-group. Condensation at the 5-amino-group under these conditions was again confirmed by the failure of the intermediate product to react with nitrous acid. The methylation of (I) was investigated, but not completely. Treatment with methyl iodide at 100° gave, amongst other things, a good yield of a dimethyl derivative. Since this compound was only sparingly soluble in water, but soluble in benzene, and since it was unaffected by treatment with nitrous acid, the 5-dimethylamino-structure (XXX) seemed the most probable.

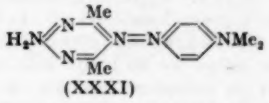
The behaviour of the diazo-compound from (I) under alkaline conditions has already been discussed. Coupling with an external end-component does occur, however, even under these conditions provided that the latter compound is sufficiently reactive (*e.g.*, β-naphthol). Where coupling is possible under acid conditions, concomitant ring-closure is avoided. Thus with dimethylaniline, a high yield of the phenylazopyrimidine (XXXI) was obtained. Normal diazo behaviour was also exhibited towards potassium iodide, with the formation of the 5-iodopyrimidine (XXXII).

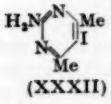
Finally, a series of diguanide derivatives of (I) was made, in which the 5-amino-group exhibited properties comparable to those of an aromatic primary amine. The pyrimidyldicyandiamide (XXXIII) was readily obtained from the diamine and dicyanimide, and this reacted with alkylamine salts to form the diguanides of type (XXXIV). Similar compounds were also obtained from the action of alkyldicyandiamides on the diamine in the manner worked out by Curd, Hendry, Kenny, Murray, and Rose (*J.*, 1948, 1630) in the proguanil series. Dr. D. G. Davey reported all the compounds made to be inactive against *P. gallinaceum* in the chick (method of Curd, Davey, and Rose, *Ann. Trop. Med. Parasit.*, 1945, **39**, 139).

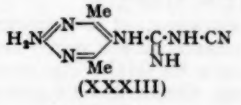
With regard to the preparation of the 5-aminopyrimidines recorded in this communication, the method worked out by Todd *et al.* (*loc. cit.*) for compound (I) was in many instances applicable, and required the condensation of a phenylazo-diketone, obtained usually in excellent yield from diazotised aniline, with a guanidine, giving 5-azopyrimidines of type (XXXV). Diguanides yielded the corresponding compound [XXXV; R^2 = H, R^1 = $C(:NH){\cdot}NH_2$]. The use of sodium ethoxide in dry ethanol, the condition employed by Todd *et al.* in the original synthesis, was found to be unnecessary. Aqueous-methanolic sodium hydroxide at 50° frequently gave better yields and in a shorter time. Reduction of (XXXV) to the 5-aminopyrimidines was by hydrogen and Raney nickel under pressure, and the yields were nearly quantitative. Of the preparations

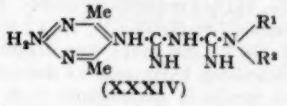

(XXIX)

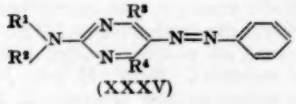

(XXX)

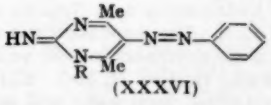

(XXXI)


(XXXII)


(XXXIII)


(XXXIV)


(XXXV)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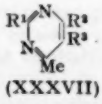
(XXXVII)

achieved in this way, that of compounds related to (XXXV; R^1 = H, R^2 = alkyl) alone seemed ambiguous. The possibility here existed that primary condensation of a monoalkylguanidine with a phenylazo-diketone might give rise exclusively, or additionally, to the

isomer (XXXVI) (cf. Majima, *Ber.*, 1908, **41**, 176). This possibility was largely excluded in the case of (XXXVI; R = Me), and by inference in other instances, by comparing the ultra-violet absorption of the final tetra-azaindene with that of (III) and (XIII; $R^1 = NMe_2$, R^2 = Me, R^3 = H). The spectra were all very similar.

The 5-amino-groups in (XIV; $R^1 = NH_2$, R^3 = Me, $R^2 = NMe_2$, SH, OMe, Cl, SMe, and $S{\cdot}CH_2{\cdot}CO_2H$) were introduced initially into the pyrimidine ring as nitro-groups, the intermediate used being the chloronitropyrimidine (XXXVII; $R^1 = NH_2$, R^2 = Cl, $R^3 = NO_2$). (XIV; $R^1 = NH_2$, R^2 = SH, R^3 = Me) was prepared directly from this compound by the action of excess of sodium sulphide which replaced the chlorine atom by the mercapto-group and also reduced the nitro- to an amino-group. The methylthio-derivative was obtained through the action of methanethiol on the same chloronitropyrimidine. The aminopyrimidine (XXXVII; R^1 = SMe, $R^2 = NMe_2$, $R^3 = NH_2$) required for conversion into (XIII; R^1 = H, $R^2 = NMe_2$, R^3 = H) was prepared by the reaction series (XXXVII; $R^1 = R^2$ = Cl, $R^3 = NO_2$) ⟶ (XXXVII; R^1 = Cl, $R^2 = NMe_2$, $R^3 = NO_2$) ⟶ (XXXVII; R^1 = SH, $R^2 = NMe_2$, $R^3 = NO_2$) ⟶ (XXXVII; R^1 = SMe, $R^2 = NMe_2$, $R^3 = NO_2$), followed by catalytic reduction. 2 : 5-Diamino-4-methylpyrimidine (XIV; $R^1 = NH_2$, R^2 = H, R^3 = Me) was obtained by reduction of the aforementioned (XIV; $R^1 = NH_2$, R^2 = Cl, R^3 = Me) with zinc dust in boiling dilute aqueous sodium hydroxide.

Experimental

Tetra-azaindenes.

5-Amino-7-methyl-1 : 2 : 4 : 6-tetra-azaindene (III).—2 : 5-Diamino-4 : 6-dimethylpyrimidine (138 g., 1 mol.) in water (1 l.) and concentrated hydrochloric acid (225 c.c.) was diazotised at 5—10° by the slow addition of sodium nitrite (70 g.) in water (200 c.c.). The solution of the diazonium salt was added during ¾ hour, through a capillary and below the surface, to vigorously stirred 5N-sodium hydroxide (1100 c.c.), kept below 10° with external cooling. The azo by-products formed were destroyed by heating the solution at 80° for 20 minutes with sodium hydrosulphite (dithionite) (50 g.), and the crude *tetra-azaindene* (123 g.; m. p. 303—304°) precipitated by adding concentrated hydrochloric acid (about 350 c.c.) until neutral to litmus. It crystallised from dimethylformamide in straw-coloured needles, m. p. 301° (decomp.) (inserted at 290°) (Found: C, 48·35; H, 4·7; N, 46·6. $C_6H_7N_5$ requires C, 48·3; H, 4·7; N, 47·0%). Addition of acetone to a solution of the base in 2N-hydrochloric acid gave a crystalline *hydrochloride*, m. p. 253° (decomp.) (Found: C, 38·3; H, 4·2; N, 37·6; Cl, 18·65. $C_6H_7N_5$,HCl requires C, 38·8; H, 4·3; N, 37·7; Cl, 19·1%). The free base was only sparingly soluble in common organic solvents and water. Dilute solutions showed strong fluorescence. It dissolved readily in dilute aqueous sodium hydroxide, but not in sodium carbonate or dilute ammonia solution.

The *azo* by-product in this reaction was made in good yield by adding the diazotised aminopyrimidine to aqueous ammonia (or sodium carbonate) in place of the sodium hydroxide. It formed red-brown plates from acetic acid, which did not melt at <340° (Found: C, 48·6; H, 4·7; N, 45·8. $C_{12}H_{14}N_{10}$ requires C, 48·3; H, 4·7; N, 47·0%).

5-Hydroxy-7-methyl-1 : 2 : 4 : 6-tetra-azaindene.—This compound slowly separated as the free *base* when the above 5-amino-7-methyl-1 : 2 : 4 : 6-tetra-azaindene (4 g.) was heated under reflux for 20 hours with concentrated hydrochloric acid (10 c.c.). It crystallised from water in colourless needles, m. p. 339° (decomp.) (Found: C, 40·9; H, 5·35; N, 32·6. $C_6H_6ON_4$,$1\frac{1}{2}H_2O$ requires C, 40·65; H, 5·1; N, 31·65%).

5-Amino-7-methylthio-1 : 2 : 4 : 6-tetra-azaindene.—2 : 5-Diamino-4-methyl-6-methylthiopyrimidine (68 g., 0·4 mol.) was diazotised (diazonium salt partly out of solution) and added to aqueous sodium hydroxide as described above for (III). The reaction mixture was heated to 50° and similarly decolorised with sodium dithionite. Caustic alkalinity was reduced by adding concentrated hydrochloric acid (75 c.c.) and finally removed with ammonium chloride (70 g.) in water (300 c.c.). The suspension was cooled and the crude *product* (32 g.) collected. It crystallised from 2-ethoxyethanol in pale yellow prisms, m. p. 269° (decomp.) (inserted at 260°) (Found: C, 40·45; H, 4·2; N, 36·7. $C_6H_7N_5S$ requires C, 39·75; H, 3·9; N, 38·7%). The *hydrochloride* crystallised from water and was not molten at 350° (Found: C, 32·05; H, 4·1; N, 31·6. $C_6H_7N_5S$,HCl,$\frac{1}{2}H_2O$ requires C, 31·8; H, 3·95; N, 30·9%). Ring-closure also occurred when the diazonium salt was heated in acid solution at 80—85° for 1½ hours. There was little or no evolution of nitrogen, but unwanted by-products were separated by dissolving

TABLE 2. *5-Phenylazopyrimidines.*

Compound no.	Substituent in position 2	Reaction notes	Solvent *	M. p.	Formula	Found, % C	Found, % H	Found, % N	Required, % C	Required, % H	Required, % N
1	Me_2N	5 Days at 20—25°	Pet, A	99°	$C_{14}H_{17}N_5$	64·3	6·3	27·25	65·9	6·7	27·4
2	EtNH	,, ,,	Pet, B	122	$C_{14}H_{17}N_5$	64·1	6·0	27·2	65·9	6·7	27·4
3	Pr^nNH	3 Days at 37°	MeOH	136	$C_{15}H_{19}N_5$	67·3	6·7	26·4	66·9	7·1	26·0
4	Pr^iNH	7 Days at 20—25°	Aq. MeOH	75—76	$C_{15}H_{19}N_5$	67·25	6·9	26·45	66·9	7·1	26·0
5	Bu^nNH	3 Days at 37°	MeOH	89	$C_{16}H_{21}N_5$	67·0	7·1	25·0	67·85	7·4	24·75
6	Bu^iNH	,,	,,	104	$C_{16}H_{21}N_5$	67·6	7·2	25·7	67·85	7·4	24·75
7	n-$C_5H_{11}NH$	Solid NaOH used; 3 days at 37°	,,	92—93	$C_{17}H_{23}N_5$	68·55	7·95	23·65	68·7	7·7	23·6
8	$[CH_2]_5>N$	3 Days at 37°	BuOH	107	$C_{17}H_{21}N_5$	69·05	7·0	24·0	69·15	7·1	23·75
9	p-Cl·C_6H_4·NH	,,	EtOH	126—127	$C_{16}H_{16}N_5Cl$	64·25	4·8	20·3	64·0	4·75	20·75
10	p-MeO·C_6H_4·NH	,,	C_6H_6–Pet	128—130	$C_{16}H_{19}ON_5$	69·0	5·8	22·3	68·5	5·7	21·0
11	NH_2–C(=NH)–NH	From diguanide sulphate, 5 mins. at 70°, then 16 hours at 45°	BuOH	247—248	$C_{12}H_{15}N_7$	57·7	5·7	36·4	57·95	5·7	36·45

TABLE 3. *5-Aminopyrimidines.*

Compound no.	Substituent in position 2	4	6	Isolation †	Solvent *	M. p.	Formula	Found, % C	Found, % H	Found, % N	Required, % C	Required, % H	Required, % N
1	Me_2N	Me	Me	Steam; base	Pet, A	122°	$C_8H_{14}N_4$	57·7	8·1	33·55	57·85	8·45	33·75
2	EtHN	Me	Me	Steam; sulphate	EtOH	145	$C_8H_{14}N_4,H_2SO_4,H_2O$	34·75	5·65	19·4	34·05	6·4	19·85
				base	Pet, A	72	$C_8H_{14}N_4$	57·95	7·9	33·3	57·85	8·45	33·7
3	Pr^iHN	Me	Me	Steam; base	,,	101	$C_9H_{16}N_4$	58·9	8·2	31·05	60·0	8·9	31·1
4	Pr^nHN	Me	Me	Steam; base	Pet, B	98	$C_9H_{16}N_4$	60·0	9·2	31·95	60·0	8·9	31·1
5	Bu^nHN	Me	Me	Steam; sulphate	H_2O	150	$C_{11}H_{18}N_4,H_2SO_4,\frac{1}{2}H_2O$	39·7	7·0	19·35	39·9	7·0	18·6
6	Bu^iHN	Me	Me	Steam; sulphate	,,	150	$C_{10}H_{18}N_4,H_2SO_4,\frac{1}{2}H_2O$	39·5	7·0	17·65	39·9	7·0	18·6
7	n-C_5H_{11}·NH	Me	Me	Steam; sulphate	,,	143—144	$C_{16}H_{20}N_4,H_2SO_4$	42·1	7·15	18·2	43·15	7·2	18·3
8	$[CH_2]_5>N$	Me	Me	Steam; base	MeOH	160—162	$C_{11}H_{18}N_4$	64·5	8·5	27·85	64·1	8·7	27·2
9	p-Cl·C_6H_4·NH	Me	Me	Steam; base	PhMe	132	$C_{12}H_{13}N_4Cl$	58·35	5·35	22·7	57·95	5·25	22·55
10	p-MeO·C_6H_4·NH	Me	Me	Benzene	,,	119	$C_{13}H_{16}ON_4$	63·95	6·5	24·3	63·9	6·55	22·95
11	NH_2	Ph	Me	Steam; base	$COMe_2$	146	$C_{11}H_{12}N_4$	66·1	6·05	27·95	66·0	6·0	28·0
12	NH_2	Pr^n	Me	Steam; base	C_6H_6	114—116	$C_8H_{14}N_4$	57·5	8·0	34·85	57·85	8·45	33·75
13	NH_2	Et	Me	Steam; ether	PhMe	132	$C_7H_{12}N_4$	55·05	7·55	36·5	55·2	7·9	36·85
14	NH_2	Et	Et	Steam; excess of NaOH	C_6H_6	98	$C_8H_{14}N_4$	58·55	8·2	33·5	57·85	8·45	33·75

* Pet, A = light petroleum, b. p. 60—80°; B, b. p. 100—120°.

† Steam = steam-distillation.

out the required tetra-azaindene in dilute aqueous sodium hydroxide. The product was obtained in a much smaller yield.

The diazonium salt was obtained in solid form by filtration of the cold diazonium suspension, and recrystallised from water without appreciable decomposition as large straw-coloured prisms which decomposed, without melting, at 180° (Found: C, 30·0; H, 4·4; N, 28·9; Cl^-, 14·7. $C_6H_8N_5SCl,1{\cdot}25H_2O$ requires C, 30·0; H, 4·4; N, 29·2; Cl^-, 14·8%). It coupled vigorously with *m*-phenylenediamine and alkaline R-salt.

5-Amino-7-hydroxy-1 : 2 : 4 : 6-tetra-azaindene.—The above 7-methylthio-compound (4·5 g.) was dissolved in hot acetic acid (40 c.c.) and perhydrol (15 c.c.) cautiously added. After continued heating at 90—95° for 1 hour the crystalline precipitate of *5-amino-7-hydroxy-1 : 2 : 4 : 6-tetra-azaindene methanesulphonate* was collected (4 g.). It crystallised slowly from water in pale yellow prisms, m. p. 370° (decomp.) (inserted at 360°) (Found: C, 28·8; H, 3·65; N, 27·95; S, 12·3. $C_5H_5ON_5,CH_3{\cdot}SO_3H$ requires C, 29·15; H, 3·65; N, 28·35; S, 12·95%).

5-Amino-7-benzylthio-1 : 2 : 4 : 6-tetra-azaindene.—2 : 5-Diamino-4-benzylthio-6-methylpyrimidine (6·2 g., 0·025 mol.) was diazotised and treated with sodium hydroxide in the manner described above. The resultant solution was treated with charcoal, and the *product* (2·25 g.) precipitated by an excess of ammonium chloride. Crystallised from chlorobenzene, it had m. p. 198° (Found: C, 56·0; H, 3·85; N, 26·65. $C_{12}H_{11}N_5S$ requires C, 56·05; H, 4·3; N, 27·1%).

5-Amino-1 : 2 : 4 : 6-tetra-azainden-7-ylthioacetic Acid.—2 : 5-Diamino-4-methyl-6-pyrimidylthioacetic acid (22 g., 0·1 mol.) in N-hydrochloric acid (250 c.c.) was diazotised and added as before to 2·5N-sodium hydroxide (200 c.c.) at 5°. Addition of excess of acetic acid precipitated the crude *tetra-azaindene* (5 g.). It was insoluble in organic solvents and did not melt. A pure specimen was prepared by adding dilute acetic acid to a solution in dilute aqueous ammonia (charcoal) (Found: C, 34·35; H, 3·95; N, 28·05. $C_7H_7O_2N_5S,H_2O$ requires C, 34·6; H, 3·7; N, 28·8%).

5 : 7-Diamino-1 : 2 : 4 : 6-tetra-azaindene.—5-Amino-7-methylthio-1 : 2 : 4 : 6-tetra-azaindene (5 g.) and ammonia (15 c.c.; *d* 0·88) were heated in a sealed tube at 150° for 16 hours. The free base (2·8 g.), m. p. 330° (decomp.), which crystallised on cooling was insoluble in organic solvents but fairly soluble in water. When added to dilute hydrochloric acid the sparingly soluble *hydrochloride* was formed which crystallised from water in infusible colourless rosettes (Found: C, 29·65; H, 4·55; N, 41·0. $C_5H_6N_6,HCl,H_2O$ requires C, 29·35; H, 4·4; N, 41·05%). The 7-benzylthiotetra-azaindene also gave the diamine under the same reaction conditions.

5-Amino-7-isopropylamino-1 : 2 : 4 : 6-tetra-azaindene.—5-Amino-7-methylthio-1 : 2 : 4 : 6-tetra-azaindene (10 g.) reacted similarly with *iso*propylamine (20 c.c.), and the residue after evaporation to dryness was extracted with dilute hydrochloric acid. The clarified suspension was treated with excess of sodium hydrogen sulphite solution. The product was obtained as the free *base* by dissolving the crystalline hydrogen sulphite, which separated, in dilute sodium hydroxide and adding excess of ammonium chloride. It crystallised from water in colourless prisms, m. p. 246° (Found: C, 47·25; H, 6·5; N, 41·5. $C_8H_{12}N_6,\frac{1}{2}H_2O$ requires C, 47·75; H, 6·45; N, 41·6%).

5-Amino-7-piperidino-1 : 2 : 4 : 6-tetra-azaindene.—5-Amino-7-benzylthio-1 : 2 : 4 : 6-tetra-azaindene (5 g.) and piperidine (5 c.c.) were heated under reflux for 4 hours. The semi-solid *product* left after treatment of the reaction mixture with benzene crystallised from dioxan in colourless prisms, m. p. 224° (decomp.) (Found: C, 54·45; H, 6·3; N, 37·35. $C_{10}H_{14}N_6$ requires C, 55·0; H, 6·4; N, 38·5%).

5-Amino-7-morpholino-1 : 2 : 4 : 6-tetra-azaindene.—Prepared similarly by using morpholine (5 g.), the *base* crystallised from water in slightly hydrated pale cream-coloured needles, m. p. 229—232° (Found: C, 47·4; H, 5·65; N, 36·95. $C_9H_{12}ON_6,0{\cdot}33H_2O$ requires C, 47·1; H, 5·6; N, 37·15%).

5-Amino-7-dimethylamino-1 : 2 : 4 : 6-tetra-azaindene.—(*a*) 2 : 5-Diamino-4-dimethylamino-6-methylpyrimidine (4·2 g.) in N-hydrochloric acid (100 c.c.) was diazotised and added to 3N-sodium hydroxide (70 c.c.) below 10°. Crystals of the sodium salt of the *product* began to separate, and after addition of 10N-sodium hydroxide (50 c.c.) they were collected and redissolved in hot water and the solution (charcoal) neutralised with acetic acid. The solid (4 g.) formed yellow crystals, m. p. 264° (decomp.), from dimethylformamide (Found: C, 42·75; H, 5·65; N, 42·25. $C_7H_{10}N_6,H_2O$ requires C, 42·85; H, 6·1; N, 42·85%).—(*b*) The diazo-solution similarly prepared from the diamine (2·7 g.) was kept at 95—100° for 10 minutes. After the colour reaction (yellow) given with *m*-phenylenediamine was no longer obtainable, excess of sodium acetate was added; the tetra-azaindene (2 g.), identical with the above, crystallised out.

7-Methyl-5-methylamino-1 : 2 : 4 : 6-tetra-azaindene.—The solution obtained by adding diazotised 5-amino-4 : 6-dimethyl-2-methylaminopyrimidine sulphate (25 g.) to 3N-sodium hydroxide (150 c.c.) was heated to 60° with the addition of sodium dithionite (3 g.), treated with charcoal, and filtered. The *product* (11·3 g.) separated when the filtrate was neutralised with hydrochloric acid, and was obtained as colourless prisms, m. p. 276—277°, when reprecipitated from dilute solution in aqueous sodium hydroxide with acetic acid (Found: C, 51·05; H, 5·4; N, 42·5. $C_7H_9N_5$ requires C, 51·55; H, 5·5; N, 42·95%).

5-Dimethylamino-7-methyl-1 : 2 : 4 : 6-tetra-azaindene.—5-Amino-2-dimethylamino-4 : 6-dimethylpyrimidine (15 g.) was converted into the tetra-azaindene in the same way, but more sodium dithionite (10 g.) was used and the *product* precipitated initially as the *hydrogen sulphite* which crystallised from water in needles, m. p. 174—176° (Found: C, 36·25; H, 5·15; N, 26·8. $C_8H_{11}N_5,H_2SO_3$ requires C, 37·05; H, 5·0; N, 27·0%). The *base* (6·4 g.) was obtained by decomposition of this salt in boiling dilute hydrochloric acid, and neutralisation with aqueous ammonia. It crystallised from toluene in colourless needles, m. p. 166° (Found: C, 54·35; H, 6·1; N, 41·15. $C_8H_{11}N_5$ requires C, 54·25; H, 6·2; N, 39·55%).

5-Ethylamino-7-methyl-1 : 2 : 4 : 6-tetra-azaindene.—Prepared similarly from 5-amino-2-ethylamino-4 : 6-dimethylpyrimidine sulphate (20 g.), this *product* (7 g.) was also initially isolated as the hydrogen sulphite. It formed colourless needles (from methanol), m. p. 224° (Found: C, 54·3; H, 5·85; N, 40·0. $C_8H_{11}N_5$ requires C, 54·25; H, 6·2; N, 39·55%).

The following homologues were obtained by the same general method, except that by avoiding the use of excessive amounts of sodium dithionite as decolorant intermediate isolation of the hydrogen sulphite was avoided.

7-Methyl-5-n-propylamino-1 : 2 : 4 : 6-tetra-azaindene, pale cream prisms (from 2-ethoxyethanol), m. p. 221° (Found: C, 57·2; H, 7·05; N, 36·65. $C_9H_{13}N_5$ requires C, 56·55; H, 6·8; N, 36·65%).

7-Methyl-5-isopropylamino-1 : 2 : 4 : 6-tetra-azaindene, colourless leaflets (from toluene), m. p. 213—215° (Found: C, 56·45; H, 6·35; N, 36·8%).

5-n-Butylamino-7-methyl-1 : 2 : 4 : 6-tetra-azaindene, cream-coloured needles (from toluene), m. p. 162° (Found: C, 58·7; H, 7·1; N, 35·25. $C_{10}H_{15}N_5$ requires C, 58·55; H, 7·3; N, 34·15%).

5-isoButylamino-7-methyl-1 : 2 : 4 : 6-tetra-azaindene, cream-coloured plates (from chlorobenzene), m. p. 200° (Found: C, 57·8; H, 7·2; N, 34·2%).

5-n-Amylamino-7-methyl-1 : 2 : 4 : 6-tetra-azaindene, cream-coloured prisms (from toluene), m. p. 154° (Found: C, 60·4; H, 7·7; N, 32·2. $C_{11}H_{17}N_5$ requires C, 60·3; H, 7·75; N, 31·95%).

7-Methyl-5-piperidino-1 : 2 : 4 : 6-tetra-azaindene, colourless needles [from light petroleum (b. p. 100—120°)], m. p. 160—161° (Found: C, 60·4; H, 6·8; N, 31·75. $C_{11}H_{15}N_5$ requires C, 60·8; H, 6·9; N, 32·25%).

5-Amino-7-ethyl-3-methyl-1 : 2 : 4 : 6-tetra-azaindene (from 2 : 5-diamino-4 : 6-diethylpyrimidine), pale yellow prismatic needles (from butanol), m. p. 219° (Found: C, 55·35; H, 6·45; N, 39·7. $C_8H_{11}N_5$ requires C, 54·25; H, 6·2; N, 39·55%).

5-Guanidino-7-methyl-1 : 2 : 4 : 6-tetra-azaindene.—5-Amino-2-guanidino-4 : 6-dimethylpyrimidine (24 g., 0·14 mol.) in 3N-hydrochloric acid (140 c.c.) was diazotised and added to 3N-sodium hydroxide (270 c.c.) below 5°. The solution was neutralised with hydrochloric acid (charcoal) and filtered at the boil. The *product* (14 g.) crystallised on cooling. It crystallised from water in colourless needles, m. p. 227° (decomp.) (Found: C, 38·45; H, 4·85; N, 43·85. $C_7H_9N_7,1\frac{1}{2}H_2O$ requires C, 38·5; H, 5·5; N, 44·9%). The *sulphate* crystallised from water in pale cream-coloured needles, not molten at 330° (Found: C, 35·2; H, 4·3; N, 41·2. $C_7H_9N_7,\frac{1}{2}H_2SO_4$ requires C, 35·0; H, 4·2; N, 40·8%).

2-p-Chloroanilino-7-methyl-1 : 2 : 4 : 6-tetra-azaindene.—5-Amino-2-*p*-chloroanilino-4 : 6-dimethylpyrimidine (12·5 g., 0·05 mol.) was made into a paste in N-hydrochloric acid (125 c.c.) and diazotised with sodium nitrite at 15—20°. The solution which resulted after stirring the diazosuspension for 16 hours in 2N-sodium hydroxide (185 c.c.) was nearly neutralised with hydrochloric acid (charcoal) and treated with excess of ammonium chloride. The *product* (6·9 g.) separated. It crystallised from butanol in pale yellow prisms, m. p. 242° (Found: C, 56·25; H, 4·0; N, 26·0. $C_{12}H_{10}N_5Cl$ requires C, 55·6; H, 3·9; N, 26·95%).

7-Methyl-5-p-anisidino-1 : 2 : 4 : 6-tetra-azaindene.—Prepared similarly from 5-amino-4 : 6-dimethyl-2-*p*-anisidinopyrimidine (5·8 g.), the crude *product* (4·3 g.) crystallised from butanol in yellow prisms, m. p. 215° (Found: C, 61·1; H, 5·0; N, 27·7. $C_{13}H_{13}ON_5$ requires C, 61·15; H, 5·1; N, 27·45%).

5-Amino-7-phenyl-1 : 2 : 4 : 6-tetra-azaindene.—Similarly prepared from 2 : 5-diamino-4-methyl-6-phenylpyrimidine (2·3 g.), the crude *product* (1·6 g.) crystallised from water in lemon-yellow prismatic needles, m. p. 90—95° (effervesce at 120—140°) (Found: C, 58·2; H, 4·85; N, 31·05. $C_{11}H_9N_5,H_2O$ requires C, 57·65; H, 4·8; N, 30·55%).

Ring-closure of Diazotised 2 : 5-Diamino-4-ethyl-6-methylpyrimidine.—The diazo-solution from the diaminopyrimidine (31·5 g.) was added in the usual manner to sodium hydroxide solution (5N; 250 c.c.) below 5° and, after hydrochloric acid had been added to reduce alkalinity somewhat, it was treated with charcoal and filtered. Excess of concentrated hydrochloric acid was added to the filtrate to give a strong acid reaction. *5-Amino-3 : 7-dimethyl-1 : 2 : 4 : 6-tetra-azaindene hydrochloride* (7·5 g.) separated. It crystallised from water in straw-coloured needles, m. p. 342° (Found: C, 42·75; H, 4·95; N, 35·9. $C_7H_9N_5,HCl$ requires C, 42·1; H, 5·0; N, 35·1%). Addition of ammonium chloride to a hot solution of the hydrochloride in dilute aqueous sodium hydroxide gave the *base* as colourless needles, m. p. 327° (decomp.) (inserted at 315°) (Found: C, 51·5; H, 5·55; N, 43·15. $C_7H_9N_5$ requires C, 51·55; H, 5·5; N, 42·95%).

The filtrate from the separation of the above hydrochloride was neutralised and evaporated to dryness. Water (400 c.c.) was added to redissolve salts, and the suspension was filtered. The crude *5-amino-7-ethyl-1 : 2 : 4 : 6-tetra-azaindene* (11 g.) crystallised from 2-ethoxyethanol in flat yellow needles (7 g.), m. p. 278—280° (inserted at 273°) (Found: C, 51·4; H, 5·5; N, 43·9. $C_7H_9N_5$ requires C, 51·55; H, 5·5; N, 42·95%).

7-Dimethylamino-5-methylthio-1 : 2 : 4 : 6-tetra-azaindene.—5-Amino-4-dimethylamino-6-methyl-2-methylthiopyrimidine (19·8 g.) in water (50 c.c.) and concentrated hydrochloric acid (22 c.c.) was diazotised at 20° with sodium nitrite (7 g.) in water (20 c.c.). The diazo-solution was heated to 95—100° for 10 minutes. The hydrochloride of the tetra-azaindene (23 g.) crystallised on cooling. The *base* was obtained by adding acetic acid to a solution of the hydrochloride in dilute aqueous sodium hydroxide. It formed rectangular prisms (from dimethylformamide), not molten at 300° (Found: C, 45·65; H, 5·15; N, 32·95. $C_8H_{11}N_5S$ requires C, 45·95; H, 5·25; N, 33·5%). In a separate experiment ring-closure occurred giving a similar yield, when the diazo-solution was kept for 2 days at 20—25°.

7-Dimethylamino-1 : 2 : 4 : 6-tetra-azaindene.—The above 5-methylthio-1 : 2 : 4 : 6-tetra-azaindene (50 g.) was stirred and heated at 100—105° for 16 hours with Raney nickel (210 g.) in dimethylformamide (330 c.c.) and water (80 c.c.). The suspension was filtered while hot, and the filtrate treated with charcoal and then evaporated to dryness under reduced pressure. Treatment of the solid with cold water (300 c.c.) and addition of concentrated hydrochloric acid precipitated the sparingly soluble hydrochloride of unchanged starting material. The solution obtained by filtration was evaporated to dryness, giving the *hydrochloride* (28 g.; m. p. 277—278°) of 7-dimethylamino-1 : 2 : 4 : 6-tetra-azaindene. Recrystallised from aqueous acetone it had m. p. 288° (Found: C, 42·05; H, 4·4; N, 33·6. $C_7H_9N_5,HCl$ requires C, 42·1; H, 4·5; N, 35·1%). The *base*, obtained by careful neutralisation of a concentrated solution in water of the hydrochloride, formed colourless prisms (from 2-ethoxyethanol), m.p. 261—264° (Found: C, 52·0; H, 5·3; N, 42·4. $C_7H_9N_5$ requires C, 51·55; H, 5·5; N, 42·9%).

In an attempt to replace the dimethylamino-group by hydroxyl, the above hydrochloride (4·5 g.) was heated under reflux for 6 hours in 5N-hydrochloric acid. The solution was neutralised with aqueous ammonia and then made just acid with acetic acid. A crystalline solid (1·1 g.) was slowly precipitated. It was insoluble in organic solvents but was purified by neutralising with acetic acid a solution (charcoal) in dilute aqueous ammonia. The product, believed to be *4-aminopyrazole-6-carboxylic acid*, decomposed at 211° (Found: C, 37·55; H, 3·9; N, 32·85. $C_4H_5O_2N_3$ requires C, 37·8; H, 3·95; N, 33·1%). It dissolved in dilute hydrochloric acid, aqueous sodium hydroxide, or ammonia, and formed a diazonium compound (coupling with β-naphthol) with nitrous acid.

Diazouracil-6-aldoxime.—A solution of 5-amino-6-methyluracil (28 g., 0·2 mol.) in N-sodium hydroxide (200 c.c.) containing sodium nitrite (28 g.) was added to 2·5N-hydrochloric acid (400 c.c.) stirred at 15—20°. The white crystalline precipitate (40 g.) was filtered off. It crystallised from water in colourless needles, m. p. 245°, which were dried at 100° (Found: C, 30·3; H, 2·55; N, 34·9. Found, in material dried at 130°/0·5 mm.: C, 30·5; H, 2·5; N, 36·5; in material dried at 160°/0·5 mm.: C, 30·5; H, 2·55; N, 35·5%. $C_5H_3O_3N_5,H_2O$ requires C, 30·15; H, 2·5; N, 35·15%). After being dried azeotropically in boiling dichlorobenzene it had m. p. 239° (decomp.) (Found: C, 33·45; H, 2·15; N, 38·5. $C_5H_3O_3N_5$ requires C, 33·15; H, 1·65; N, 38·7%). Recrystallisation from water re-formed the *hydrate* (Found: C, 30·05; H, 2·5; N, 35·2%).

Miscellaneous Compounds related to the Foregoing Tetra-azaindenes.

2 : 6-*Diamino-5-formamido-4-methylpyrimidine*.—2 : 5 : 6-Triamino-4-methylpyrimidine (5 g.) and formic acid (98%; 15 c.c.) were refluxed for 7 hours, and the crystalline solid which formed on addition of ether was dissolved in hot water and made alkaline with aqueous ammonia. The precipitate of the *base* (3·2 g.) crystallised from water in colourless needles which melted below 300° only when heated rapidly (Found: C, 42·5; H, 5·45; N, 42·05. Calc. for $C_6H_9ON_5$: C, 43·1; H, 5·4; N, 41·9%).

2-*Amino-6-methylpurine*.—The above formamidopyrimidine (3 g.) was powdered and added to paraffin (80 c.c.) previously heated to 280°. After evolution of gas had ceased (5 minutes), the suspension was diluted with benzene and filtered off. Addition of saturated aqueous ammonium chloride to a solution of the solid (2·3 g.) in 0·5N-sodium hydroxide (20 c.c.) (charcoal) gave the product as colourless needles (1·8 g.). It crystallised from water, and when heated sintered and decomposed at 300—320° (Found: C, 48·1; H, 4·65; N, 48·5. Calc. for $C_6H_7N_5$: C, 48·3; H, 4·7; N, 47·0%).

2-*Amino*-4 : 6 : 7-*trimethylpteridine*.—Addition of diacetyl (4 g.) to a solution at 80° of 2 : 5 : 6-triamino-4-methylpyrimidine (6 g.) in water (50 c.c.) gave immediate precipitation of the *product* (4·5 g.) which crystallised from 2-ethoxyethanol in yellow plates, m. p. 312—313° (Found: C, 56·6; H, 5·9; N, 36·2. $C_9H_{11}N_5$ requires C, 57·15; H, 5·8; N, 37·05%).

2-*Amino-6-methyl*-1′ : 2′ : 3′-*triazolo*(5′ : 4′-4 : 5)*pyrimidine*.—The crystalline precipitate which formed when sodium nitrite (3·5 g.) in water (30 c.c.) was added to a cooled solution of 2 : 5 : 6-triamino-4-methylpyrimidine (7 g.) in 2N-hydrochloric acid (75 c.c.) was redissolved in dilute aqueous sodium hydroxide. Addition of acetic acid reprecipitated the *product* (7·4 g.) which crystallised from much water in colourless plates, m. p. 284—285° (Found: C, 35·7; H, 5·2; N, 49·8. $C_5H_6N_6,H_2O$ requires C, 35·7; H, 4·8; N, 50·0%).

2-*Amino-6-methyl*-1′ : 2′ : 3′-*oxadiazolo*(5′ : 4′-4 : 5)*pyrimidine*.—2 : 5-Diamino-4-hydroxy-6-methylpyrimidine (7·9 g.), prepared by catalytic reduction under pressure with Raney nickel and hydrogen of the azo-compound obtained by the action of diazotised *p*-chloroaniline on 2-amino-4-hydroxy-6-methylpyrimidine (Jaeger, *Annalen*, 1891, **262**, 365), was dissolved in 2N-hydrochloric acid (100 c.c.) and treated at 10° with sodium nitrite (3·5 g.) in water (20 c.c.). The solution was made alkaline with ammonia, whereupon the *oxadiazole* (5·7 g.) crystallised in cream-coloured needles which decomposed explosively at about 150° (Found: C, 40·7; H, 3·55; N, 46·5. $C_5H_5ON_5$ requires C, 39·8; H, 3·3; N, 46·4%).

2-*Amino-6-methyl*-1′ : 2′ : 3′-*thiadiazolo*(5′ : 4′-4 : 5)*pyrimidine*.—The suspension which formed when sodium nitrite (17 g.) in water (50 c.c.) was added to a cooled solution of 2 : 5-diamino-4-methyl-6-mercaptopyrimidine (39 g.) in 2N-hydrochloric acid (375 c.c.) was kept overnight and filtered. The solid crystallised from dimethylformamide, to give the *product* in colourless needles (23·2 g.), m. p. 216° (Found: C, 36·0; H, 3·0; N, 41·9. $C_5H_5N_5S$ requires C, 35·9; H, 3·0; N, 41·9%).

2-*Amino-6-methyl*-1′ : 3′-*thiazolo*(5′ : 4′-4 : 5)*pyrimidine*.—The solution which formed when 2 : 5-diamino-4-methyl-6-mercaptopyrimidine (5 g.) and formic acid (98%; 20 c.c.) were refluxed for 7 hours, was diluted with water (100 c.c.), treated with charcoal, and made strongly alkaline with aqueous sodium hydroxide. The *product* was collected (3·5 g.) and crystallised from butanol; it had m. p. 214° (Found: C, 43·25; H, 3·7; N, 34·75. $C_6H_6N_4S$ requires C, 43·35; H, 3·6; N, 33·75%).

2 : 2′-*Diamino-6-methyl*-1′ : 3′-*thiazolo*(5′ : 4′-4 : 5)*pyrimidine*.—2 : 5-Diamino-4-chloro-6-methylpyrimidine (24 g.), potassium thiocyanate (15·6 g.), and 2N-hydrochloric acid (150 c.c.) were heated at 95° for 30 minutes, and the crystalline precipitate which formed on cooling was collected. This was recrystallised from water (charcoal), just sufficient ammonia being added to remove the acid reaction. The *hydrochloride* so obtained formed flat yellow needles (9 g.), m. p. 315° (decomp.) (Found: C, 33·9; H, 4·3; N, 34·35. $C_6H_7N_5S,HCl$ requires C, 33·1; H, 3·5; N, 32·2%). The *base* was precipitated by addition of sodium hydroxide to a solution of the hydrochloride in hot water. It crystallised from butanol in colourless plates, m. p. 276—278° (Found: C, 40·6; H, 3·85; N, 37·85; S, 17·7. $C_6H_7N_5S$ requires C, 39·8; H, 3·85; N, 38·7; S, 17·7%).

2′-*Amino*-5 : 6-*dihydro*-5-*keto*-6′-*methylpyrimidino*(4′ : 5′-2 : 3)-1 : 4-*thiazine* (XXVI).—2 : 5-Diamino-4-methyl-6-pyrimidylthioacetic acid (9·5 g.) and 2N-hydrochloric acid (120 c.c.) were refluxed for 30 minutes. Long prismatic needles (6·05 g.) of the hydrated *hydrochloride*, insoluble in dilute alkalis, separated on cooling (Found: C, 33·9; H, 4·3; N, 23·0. $C_7H_9ON_4S,HCl,H_2O$ requires C, 33·55; H, 4·4; N, 22·35%).

Preparation of 5-aminopyrimidine intermediates.

2 : 5-*Diamino*-4 : 6-*dimethylpyrimidine*.—The method of Hull, Lovell, Openshaw, and Todd (*loc. cit.*) was modified to facilitate large-scale working.

(a) **2-*Amino*-4 : 6-*dimethyl*-5-*phenylazopyrimidine*.** Aniline (186 g.) in water (400 c.c.), crushed ice (1200 g.), and 10N-hydrochloric acid (500 c.c.) was diazotised by the rapid addition of sodium nitrite (144 g.) in water (500 c.c.), and the diazo-solution was added to a stirred suspension of acetylacetone (300 g.) in water (2 l.) and anhydrous sodium carbonate (440 g.). Phenylazoacetylacetone formed rapidly and after 30 minutes it was collected and added without further treatment to guanidine nitrate (410 g.), 10N-sodium hydroxide (720 c.c.), and methanol (1600 c.c.). The mixture was stirred for 20 hours at 50°, and the azopyrimidine was collected and washed successively with methanol (500 c.c.), water (1 l. at 60°), and more methanol (200 c.c.). It was obtained as orange plates (410 g.), m. p. 227—229°. Hull, Lovell, Openshaw, and Todd (*loc. cit.*) gave m. p. 228—230°.

(b) **2 : 5-*Diamino*-4 : 6-*dimethylpyrimidine*.** The above azopyrimidine (300 g.) was suspended in methanol (500 c.c.) and reduced with hydrogen under pressure in the presence of Raney nickel (10—20 g.). After addition of water (200 c.c.) and heating to 60°, the solution of the diamine was filtered from catalyst and evaporated under reduced pressure. The residual solid was washed on to a filter with ether. It formed large colourless prisms (180 g.), m. p. 184·5—186·5°. Hull *et al.* give m. p. 183·5—184·5° for sublimed material.

Other **2 : 5-*Diaminopyrimidines*.**—Many of these, used as intermediates in this work, were prepared by processes similar to that described above. The relevant 5-phenylazopyrimidines are listed in Table 2, and the syntheses are exemplified more completely by the following details for the preparation of **4 : 6-*dimethyl*-2-*methylamino*-5-*phenylazopyrimidine***:

Methylguanidine sulphate (36 g., 0·3 mol.), methanol (200 c.c.), and 11N-sodium hydroxide (66 c.c.) were stirred until complete solution was obtained. Phenylazoacetylacetone (41 g., 0·2 mol.) was added, and, after being warmed to 50° to effect solution, the mixture was kept at 20—25° for 5 days. The *product* was then filtered off, washed successively with 50% methanol, warm water, and more 50% methanol, and crystallised from toluene. It formed golden needles, m. p. 161° (Found: C, 63·8; H, 5·85; N, 29·15. $C_{13}H_{15}N_5$ requires C, 64·75; H, 6·2; N, 29·05%).

The following additional phenylazopyrimidines were made similarly but are not conveniently tabulated.

2-*Amino*-4-*methyl*-6-*phenyl*-5-*phenylazopyrimidine*. Prepared from guanidine nitrate (20 g.), phenylazobenzoylacetone (13·5 g.), methanol (60 c.c.) and 11N-sodium hydroxide (30 c.c.) kept for 2 days at 37°, the *compound* crystallised from ethanol in red-brown prisms, m. p. 158° (Found: C, 71·5; H, 5·0; N, 24·0. $C_{17}H_{15}N_5$ requires C, 70·55; H, 5·2; N, 24·2%).

2-*Amino*-6-*ethyl*-4-*methyl*-5-*phenylazopyrimidine*. Prepared similarly from **3-*phenylazohexane*-2 : 4-*dione*** [m. p. 83—84°, from methanol (Found: C, 66·0; H, 6·0; N, 13·0. $C_{12}H_{14}O_2N_2$ requires C, 66·05; H, 6·4; N, 12·85%)], the *compound* crystallised from butanol in yellow-red needles m. p. 171° (Found: C, 64·75; H 5·1; N, 29·15. $C_{13}H_{15}N_5$ requires C, 64·75; H, 6·2; N, 29·05%).

2-*Amino*-4 : 6-*diethyl*-5-*phenylazopyrimidine*. Prepared similarly from **4-*phenylazoheptane*-3 : 5-*dione*** [m. p. 76°, from methanol (Found: C, 66·75; H, 6·7; N, 12·55. $C_{13}H_{16}O_2N_2$ requires C, 67·25; H, 6·9; N, 12·1%)], the *compound* crystallised from methanol in red plates, m. p. 156° (Found: C, 66·5; H, 6·5; N, 27·2. $C_{14}H_{17}N_5$ requires C, 65·9; H, 6·6; N, 27·45%).

2-*Amino*-6-*methyl*-5-*phenylazo*-4-n-*propylpyrimidine*. Prepared similarly from **4-*phenylazooctane*-3 : 5-*dione*** [m. p. 65°, from methanol–water (Found: C, 67·55; H, 6·65; N, 13·15. $C_{14}H_{18}O_2N_2$ requires C, 68·2; H, 7·3; N, 11·4%)], the *compound* crystallised from methanol in orange needles, m. p. 108° (Found: C, 66·0; H, 6·6; N, 27·85. $C_{14}H_{17}N_5$ requires C, 65·9; H, 6·6; N, 27·5%).

Reduction of Phenylazopyrimidines.—This was effected in all cases catalytically with hydrogen at or above atmospheric pressure over Raney nickel, and with methanol as solvent. After filtration from catalyst, the solvent was removed and the residue crystallised either as the base or as a salt such as the sulphate after (*a*) treatment with a solvent such as benzene or ether, or (*b*) with steam, to remove the aniline formed. Some of the bases were very soluble in water and when isolated as such required the addition of a large excess of sodium hydroxide. The methods used to prepare the diamines listed in Table 3 are exemplified by the following preparations. In the table, reduction was under pressure unless otherwise noted.

5-*Amino*-2-*guanidino*-4 : 6-*dimethylpyrimidine*. 2-Guanidino-4 : 6-dimethyl-5-phenylazopyrimidine (26·2 g.) in methanol (150 c.c.) was reduced at N.T.P. After filtration from

catalyst and removal of solvent, the pasty product was extracted twice with boiling benzene. The residue was dissolved at 80° in sufficient N-sulphuric acid, and on cooling the *sulphate* crystallised in colourless needles (14 g.), m. p. 229° (Found: C, 29·1; H, 5·3; N, 30·4. $C_7H_{12}N_6,H_2SO_4$ requires C, 30·2; H, 5·0; N, 30·2%).

5-Amino-4 : 6-dimethyl-2-methylaminopyrimidine. 4 : 6-Dimethyl-2-methylamino-5-phenylazopyrimidine (35 g.) was reduced in methanol, initially at 35° and under pressure. The filtrate from separation of the catalyst was steam-distilled to remove both solvent and aniline. 5N-Sulphuric acid was added to the aqueous solution to give a strong acid reaction and the *sulphate* was precipitated. It crystallised from water in colourless needles, m. p. 193° (Found: C, 32·2; H, 5·85; N, 22·05. $C_7H_{13}N_4,H_2SO_4$ requires C, 33·6; H, 5·6; N, 22·4%). The *base*, prepared by the action of aqueous sodium hydroxide on the sulphate, crystallised from xylene in colourless prisms, m. p. 113° (Found: C, 54·9; H, 7·2; N, 36·75. $C_7H_{12}N_4$ requires C, 55·25; H, 7·9; N, 36·85%).

2 : 5-*Diamino-4-dimethylamino-6-methylpyrimidine.*—Dimethylamine (25% aqueous solution, 40 c.c.) was added to 2-amino-4-chloro-6-methyl-5-nitropyrimidine (19 g.) in dioxan (50 c.c.) initially at 40°. Crystals of *2-amino-4-dimethylamino-6-methyl-5-nitropyrimidine* separated on cooling, and recrystallised from ethanol in golden needles, m. p. 192—193° (Found: C, 42·45; H, 5·55; N, 35·95. $C_7H_{11}O_2N_5$ requires C, 42·65; H, 5·55; N, 35·55%). This nitro-compound (15 g.) was reduced in methanol by hydrogen under pressure in the presence of Raney nickel, and 2 : 5-*diamino-4-dimethylamino-6-methylpyrimidine* (11 g.) crystallised from benzene in colourless prisms, m. p. 117—119° (Found: C, 50·55; H, 7·6; N, 41·6. $C_7H_{13}N_5$ requires C, 50·3; H, 7·8; N, 41·9%).

2 : 5-*Diamino-4-mercapto-6-methylpyrimidine.*—2-Amino-4-chloro-6-methyl-5-nitropyrimidine (19 g.) was added portionwise to a stirred melt of sodium sulphide nonahydrate (70 g.) at 95°. After a further 1 hour at this temperature, the mixture was cooled and the crystalline sodium salt of the mercaptopyrimidine collected. Almost pure *product* was precipitated when acetic acid was added to a solution of the salt in hot water. Crystallised from 2-ethoxyethanol–water, it had m. p. 310° (decomp.) (Found: C, 38·85; H, 5·25; N, 36·15. $C_5H_6N_4S$ requires C, 38·45; H, 5·15; N, 35·9%).

2 : 5-*Diamino-4-methyl-6-methylthiopyrimidine.*—10N-Sodium hydroxide (14 c.c.) was added to a suspension, kept at 50°, of 2-amino-4-chloro-6-methyl-5-nitropyrimidine (4 g.) and *S*-methylthiuronium sulphate (6 g.) in dioxan (20 c.c.) and water (20 c.c.). After 15 minutes, the crude *2-amino-4-methyl-6-methylthio-5-nitropyrimidine* (3 g.) was filtered off. It crystallised from butanol in yellow needles, m. p. 219° (Found: C, 36·25; H, 3·95; N, 27·05. $C_6H_6O_2N_4S$ requires C, 36·0; H, 4·0; N, 28·0%), and was reduced in methanolic solution with hydrogen under pressure over palladium on carbon. The 2 : 5-*diamino-4-methyl-6-methylthiopyrimidine* so obtained crystallised from water in colourless prisms, m. p. 141—142° (Found: C, 41·85; H, 5·9; N, 34·0. $C_6H_{10}N_4S$ requires C, 42·35; H, 5·9; N, 33·0%).

2 : 5-*Diamino-4-benzylthio-6-methylpyrimidine.*—*2-Amino-4-benzylthio-6-methyl-5-nitropyrimidine* [yellow prismatic needles from benzene, m. p. 155° (Found: C, 53·2; H, 4·4; N, 20·25. $C_{12}H_{12}O_2N_4S$ requires C, 52·2; H, 4·35; N, 20·3%)] was obtained similarly from *S*-benzylthiuronium chloride, and, reduced catalytically in butanol, gave the *diamine*, m. p. 160° (Found: C, 59·15; H, 6·0; N, 23·0. $C_{12}H_{14}N_4S$ requires C, 58·6; H, 5·7; N, 22·8%).

2 : 5-*Diamino-4-methyl-6-pyrimidylthioacetic Acid.*—2 : 5-Diamino-6-mercapto-4-methylpyrimidine (37 g.), chloroacetic acid (24 g.), and 2N-sodium hydroxide (300 c.c.) were heated together at 95° for 30 minutes. Addition of excess of acetic acid precipitated the *product* (48·5 g.) which was further purified by reprecipitation from alkaline solution. It formed cream-coloured needles, decomp. about 230° (Found: C, 35·85; H, 5·35; N, 25·2. $C_7H_{10}O_2N_4S,H_2O$ requires C, 36·2; H, 5·15; N, 24·1%).

5-Amino-4-dimethylamino-6-methyl-2-methylthiopyrimidine.—(a) *2-Chloro-4-dimethylamino-6-methyl-5-nitropyrimidine.* Dimethylamine (162 c.c.; 25% aqueous solution), neutralised to litmus by the addition of glacial acetic acid, was added to 2 : 4-dichloro-6-methyl-5-nitropyrimidine (62 g.) suspended in dioxan (240 c.c.) at 20°, and stirred at that temperature overnight. The crude *product* obtained by the addition of water gave golden needles (33·5 g.), m. p. 97—98°, from methanol (Found: C, 38·9; H, 4·05; N, 25·6. $C_7H_9O_2N_4Cl$ requires C, 38·8; H, 4·15; N, 25·85%).

(b) *4-Dimethylamino-2-mercapto-6-methyl-5-nitropyrimidine.* Glacial acetic acid (30 g.) in methanol (100 c.c.) was added slowly to sodium sulphide nonahydrate (120 g.) in methanol (250 c.c.) kept below 20°, and the solution was added to the above chloronitropyrimidine (54 g.) dissolved in methanol (300 c.c.) at 40°. The mixture was warmed to 65° for several

minutes, the *thiol* beginning to separate. Precipitation was completed by addition of water and acidification with acetic acid. The product (45 g.; m. p. 225°), collected and recrystallised from acetic acid, formed lemon-yellow needles, m. p. 224° (Found: C, 39·15; H, 4·9; N, 25·65. $C_7H_{10}O_2N_4S$ requires C, 39·25; H, 4·65; N, 26·15%).

(c) *4-Dimethylamino-6-methyl-2-methylthio-5-nitropyrimidine.* Methyl sulphate (30 c.c.) was added portionwise to the above thiol (43 g.) dissolved and stirred in 2N-sodium hydroxide (500 c.c.) at 20°. After 30 minutes, the crystalline *methylthiopyrimidine* was collected and recrystallised from light petroleum (b. p. 60—80°). It formed yellow prisms, m. p. 78° (Found: C, 42·25; H, 5·5; N, 24·5. $C_8H_{12}O_2N_4S$ requires C, 42·1; H, 5·25; N, 24·55%). Reduction of this product (18 g.) in methanol with hydrogen over Raney nickel at N.T.P. gave the required *5-amino-4-dimethylamino-6-methyl-2-methylthiopyrimidine* (16 g.) which formed colourless needles, m. p. 70°, from light petroleum (b. p. 80—100°) (Found: C, 48·9; H, 7·4; N, 28·25. $C_8H_{14}N_4S$ requires C, 48·5; H, 7·05; N, 28·3%).

2 : 5-Diamino-4-methoxy-6-methylpyrimidine.—(a) *2-Amino-4-methoxy-6-methyl-5-nitropyrimidine.* The solution obtained by adding 2-amino-4-chloro-6-methyl-5-nitropyrimidine (19 g.) to sodium (4·6 g.) dissolved in methanol (150 c.c.) was refluxed for 15 mintues and cooled to 0°. The crystalline precipitate of *methoxy*-compound was filtered off, washed with water (yield 17 g.), and recrystallised from 2-ethoxyethanol in yellow needles, m. p. 199° (Found: C, 39·2; H, 4·5; N, 30·85. $C_6H_8O_3N_4$ requires C, 39·15; H, 4·35; N, 30·45%).

(b) 2 : 5-Diamino-4-methoxy-6-methylpyrimidine resulted from the reduction of the nitro-compound (9·2 g.) in methanol with hydrogen over Raney nickel at N.T.P. The diamine was precipitated as the *sulphate* (10·4 g.) by adding 10N-sulphuric acid to the solution after filtration from catalyst. It formed colourless needles (from aqueous ethanol), m. p. 167—169° (Found: C, 25·4; H, 5·5; N, 20·05. $C_6H_{10}ON_4,H_2SO_4$ requires C, 25·8; H, 4·7; N, 20·05%).

2 : 5-Diamino-4-chloro-6-methylpyrimidine.—2-Amino-4-chloro-6-methyl-5-nitropyrimidine (38 g.) was reduced in methanol (150 c.c.) with hydrogen over Raney nickel at N.T.P., requiring 20 hours. Concentrated hydrochloric acid (20 c.c.) was added to the suspension, followed by sodium acetate crystals (40 g.) dissolved in water (20 c.c.). After filtration, evaporation left a residue which when digested with a little water at 0—5° gave the crude *base* (20 g.). It formed colourless needles (from water), m. p. 198° (decomp.) (Found: C, 37·55; H, 4·7; N, 34·7. $C_5H_7N_4Cl$ requires C, 37·85; H, 4·4; N, 35·3%).

2 : 5-Diamino-4-methylpyrimidine.—The above 2 : 5-diamino-4-chloro-6-methylpyrimidine (31 g.) was added to a suspension of zinc dust (100 g.) in 4N-sodium hydroxide (300 c.c.) and refluxed (10 minutes) until completely dissolved, and the whole filtered. Addition of 10N-sodium hydroxide (400 c.c.) to the chilled filtrate gave the crude solid *base*, which formed colourless prisms, m. p. 182—183°, from a hot dioxan solution dried over solid potassium hydroxide (Found: C, 48·45; H, 6·35; N, 45·45. $C_5H_8N_4$ requires C, 48·4; H, 6·5; N, 45·1%). The base was very soluble in water giving strongly fluorescing solutions.

5-Acetamido-2-amino-4 : 6-dimethylpyrimidine.—Prepared from the diamine (13·8 g.) and acetic anhydride (12 c.c.) at 50°, and crystallised from butanol in colourless prisms, this *derivative* had m. p. 246—247° (Found: C, 53·1; H, 6·3; N, 31·9. $C_8H_{12}ON_4$ requires C, 53·3; H, 6·65; N, 31·1%).

2-Amino-5-benzamido-4 : 6-dimethylpyrimidine.—Prepared from the diamine shaken with benzoyl chloride in 2N-sodium hydroxide, the *benzoyl* derivative gave colourless prisms, m. p. 289·5—290·5°, from butanol (Found: N, 22·7. $C_{13}H_{14}ON_4$ requires N, 23·15%).

NN'-Di-(2-amino-4 : 6-dimethyl-5-pyrimidyl)urea.—Carbonyl chloride was passed into a solution of the diamine (4·6 g.) in water (75 c.c.) and sodium acetate crystals (4·6 g.) at 20—25° until no diazotisable amine remained. Addition of sodium hydroxide precipitated the urea (insoluble in common solvents, and infusible) which gave the *dihydrochloride* as colourless leaflets when a solution in 5N-hydrochloric acid was treated with excess of acetone (Found: C, 39·3; H, 5·8; N, 28·5; Cl, 17·75. $C_{13}H_{18}ON_8,2HCl,H_2O$ requires C, 39·65; H, 5·6; N, 28·4; Cl, 18·05%).

2-Amino-4 : 6-dimethyl-5-thioureidopyrimidine.—The diamine (3·5 g.), potassium thiocyanate (2·6 g.), and 3N-hydrochloric acid (17 c.c.) were heated under reflux for 30 minutes. Addition of ammonia precipitated the *thiourea*, which crystallised from 2-ethoxyethanol in colourless prismatic needles, m. p. 235° (decomp.) (Found: C, 43·05; H, 6·3; N, 34·1. $C_7H_{11}N_5S$ requires C, 42·65; H, 5·6; N, 35·5%).

Ethyl N-2-Amino-4 : 6-dimethyl-5-pyrimidyloxamate.—The diamine (10 g.) and ethyl oxalate (30 c.c.) were refluxed for 5 hours. The solid precipitated by addition of light petroleum (50 c.c.; b. p. 100—120°) was extracted with boiling ethanol (100 c.c.), and the extract evaporated to dryness. Treatment of the residue with water (50 c.c.) at 50° left the *oxamate* (3·3 g.) which

crystallised from water in colourless plates, m. p. 189—190° (Found: C, 50·65; H, 5·95; N, 24·2. $C_{10}H_{14}O_2N_4$ requires C, 50·4; H, 5·9; N, 23·5%).

NN'-Di-(2-amino-4 : 6-dimethyl-5-pyrimidyl)malondiamide.—The diamine (5·5 g.) and ethyl malonate (3·2 g.) were heated at 200—210° for 5 hours. The precipitate of crude *amide* obtained after cooling and addition of water was collected, dissolved in dilute hydrochloric acid, and reprecipitated with aqueous sodium hydroxide. It crystallised from glacial acetic acid in colourless needles (2·2 g.), m. p. 334·5° (Found: C, 51·7; H, 6·0; N, 32·35. $C_{15}H_{20}O_2N_8$ requires C, 52·3; H, 5·8; N, 32·55%).

2-Amino-4 : 6-dimethyl-5-p-nitrobenzenesulphonamidopyrimidine.—The diamine (4·4 g.), *p*-nitrobenzenesulphonyl chloride (4·4 g.), crystalline sodium acetate (4·1 g.), and water (12 c.c.) were refluxed for 2 hours, and cooled. The precipitate, collected, redissolved in dilute sodium hydroxide, and reprecipitated by acetic acid, afforded the *product* (2 g.) as pale yellow prisms (from ethanol), m. p. 230—232° (Found: C, 45·55; H, 5·05; N, 18·95. $C_{12}H_{13}O_4N_5S,C_2H_5{\cdot}OH$ requires C, 45·5; H, 5·15; N, 18·95%).

2-Amino-4 : 6-dimethyl-5-sulphanilamidopyrimidine.—The above nitro-compound was reduced by hydrogen in the presence of Raney nickel at N.T.P. The *amine* so formed crystallised from water–ethanol in rosettes of colourless needles, m. p. 280° (Found: N, 23·7. $C_{12}H_{15}O_2N_5S$ requires N, 23·9%).

2-Amino-5-dimethylamino-4 : 6-dimethylpyrimidine.—The diamine (4·6 g.), methyl iodide (4 c.c.), methanol (4 c.c.), and water (4 c.c.) were heated in a sealed tube at 100° for 4 hours. The resultant solution was evaporated to dryness. The crude *product* (3·5 g.; m. p. 132—144°) was obtained when ammonia was added to a solution of the residue in water (50 c.c.). It crystallised from toluene in colourless prisms (2 g.), m. p. 151—152° (Found: C, 57·8; H, 8·0; N, 33·1. $C_8H_{14}N_4$ requires C, 57·85; H, 8·4; N, 33·7%). The compound was unchanged after treatment in dilute hydrochloric acid solution with sodium nitrite.

2-Amino-5-p-dimethylamino-4 : 6-dimethylphenylazopyrimidine.—The diamine (13·8 g.) in 2N-hydrochloric acid (150 c.c.) was diazotised at 10° with sodium nitrite (7 g.) in water (25 c.c.). Dimethylaniline (24·2 g.) in 2N-hydrochloric acid (100 c.c.) was added, followed by sufficient sodium acetate to remove the acid reaction to Congo-red. More sodium acetate was added as required, and the mixture was stirred at 10° for 2 days until no diazo-reaction (alkaline R-salt) remained. The *azo*-compound was collected and crystallised from butanol (charcoal) in orange-brown prisms, m. p. 215—218° (Found: C, 62·05; H, 6·5; N, 31·6. $C_{14}H_{18}N_6$ requires C, 62·2; H, 6·65; N, 31·1%).

2-Amino-5-iodo-4 : 6-dimethylpyrimidine.—Potassium iodide (100 g.) was added to a diazo-solution from the diamine (70 g.) prepared as described immediately above. The crystalline suspension which formed was stirred at 85—95° until nitrogen evolution ceased. Boiling water was added, to effect complete solution, followed by excess of 10N-sodium hydroxide. The precipitate of the *iodo*-compound was collected and crystallised from toluene (charcoal) in yellow prisms (58·5 g.), m. p. 185° (Found: C, 29·65; H, 3·15; N, 17·35. $C_6H_8N_3I$ requires C, 28·9; H, 3·2; N, 16·85%).

Guanidine and Diguanide Derivatives of 2 : 5-Diamino-4 : 6-dimethylpyrimidine.—N^1-(*2-Amino-4 : 6-dimethyl-5-pyrimidyl*)-N^3-*cyanoguanidine.* The diamine (28 g.), sodium dicyanimide (20 g.), and water (50 c.c.) were warmed together to dissolve. 11N-Hydrochloric acid (19 c.c.) was added and the mixture was heated at 95° for 1½ hours. The crystals of the *dicyandiamide* which deposited were collected [27·5 g.; m. p. 278—279° (decomp.)] and gave colourless prisms, m. p. 297°, from wet 2-ethoxyethanol (Found: N, 46·5. $C_8H_{11}N_7$ requires N, 47·8%). The product was only sparingly soluble in water but dissolved in dilute hydrochloric acid or sodium hydroxide.

2-Amino-4 : 6-dimethyl-5-pyrimidyldiguanide. The diamine (9·2 g.), dicyandiamide (6 g.), and 4N-hydrochloric acid (16 c.c.) were heated under reflux for 2 hours, and then added to potassium iodide (20 g.) dissolved in water (25 c.c.). The *diguanide hydriodide* which separated on cooling recrystallised from water (charcoal) in colourless needles (8·6 g.), m. p. 276·5—277·5° (decomp.) (Found: C, 27·55; H, 4·0; N, 31·3. $C_8H_{14}N_8,HI$ requires C, 27·4; H, 4·3; N, 32·0%).

The following N^1-*alkyl*-N^5-*2-amino-4 : 6-dimethyl-5-pyrimidyldiguanide hydriodides* were prepared in a similar manner, from the appropriate alkylcyanoguanidines (Curd, Hendry, Kenny, Murray, and Rose, *loc. cit.*): N^1-*methyl-*, prismatic needles (from water), m. p. 244° (decomp.) (Found: C, 29·05; H, 4·75; N, 28·7. $C_9H_{16}N_8,HI$ requires C, 29·65; H, 4·65; N, 30·8%); N^1N^1-*dimethyl-*, colourless needles (from methanol), m. p. 254—260° (decomp.) (Found: C, 32·1; H, 5·25; N, 28·1. $C_{10}H_{18}N_8,HI$ requires C, 31·75; H, 5·05; N, 29·65%); N^1-iso-

propyl-, colourless prisms (from methanol), m. p. 257—259° (decomp.) (Found : 33·6; H, 5·4; N, 27·7. $C_{11}H_{20}N_8$,HI requires C, 33·65; H, 5·35; N, 28·55%); N^1N^1-cyclo*pentamethylene-*, colourless prisms (from water), m. p. 258° (decomp.) (Found : C, 37·6; H, 5·55; N, 25·6. $C_{13}H_{22}N_8$,HI requires C, 37·3; H, 5·5; N, 26·8%); and N^1-methyl-N^1-*iso*propyl-, isolated as *hydrochloride*, colourless prisms (from water), m. p. 263° (decomp.) (Found : C, 46·15; H, 7·35; N, 34·0. $C_{12}H_{22}N_8$,HCl requires C, 45·8; H, 7·3; N, 35·6%).

N^1-2-*Amino*-4 : 6-*dimethyl*-5-*pyrimidyl*-N^5-*ethyldiguanide*. N^1-(2-Amino-4 : 6-dimethyl-5-pyrimidyl)-N^3-cyanoguanidine (2 g.; prepared as described above), ethylamine (33% solution in water; 2·7 c.c.), acetic acid (1·8 c.c.) and 2-ethoxyethanol (3 c.c.) were heated under reflux for 7 hours. The *dihydriodide* was precipitated by dilution with water (20 c.c.) containing potassium iodide (10 g.). It gave colourless plates (from water), m. p. 304° (decomp.) (Found : C, 24·2; H, 4·5; N, 23·25. $C_{10}H_{18}N_8$,2HI requires C, 23·7; H, 3·95; N, 22·15%).

N^1N^5-*Di*-(2-*amino*-4 : 6-*dimethyl*-5-*pyrimidyl*)*diguanide*. N^1-(2-Amino-4 : 6-dimethyl-5-pyrimidyl)-N^3-cyanoguanidine (4·1 g.), 2 : 5-diamino-4 : 6-dimethylpyrimidine (2·9 g.), concentrated hydrochloric acid (1·8 c.c.), water (3 c.c.), and 2-ethoxyethanol (5 c.c.) were heated under reflux for 16 hours. The crystalline *dihydrochloride* was collected and after crystallisation twice from water gave colourless plates, m. p. 286—288° (decomp.) (Found : C, 40·65; H, 6·25; N, 35·5. $C_{14}H_{21}N_{11}$,2HCl requires C, 40·4; H, 5·55; N, 37·0%).

N^1-(2-*Amino*-4 : 6-*dimethyl*-5-*pyrimidyl*)-N^5-p-*chlorophenyldiguanide*. N^1-(2-Amino-4 : 6-dimethyl-5-pyrimidyl)-N^3-cyanoguanidine (2 g.), *p*-chloroaniline (1·4 g.), and concentrated hydrochloric acid (1 c.c.) were cautiously heated under reflux in an oil-bath for 2 hours. Water (25 c.c.) was added, and the crystals which formed were collected. The *hydrochloride* crystallised from water (2·3 g.) in rosettes of colourless needles, m. p. 259° (decomp.) (Found : C, 43·7; H, 5·4; N, 28·2. $C_{14}H_{17}N_8Cl$,HCl,H_2O requires C, 43·4; H, 5·15; N, 28·95%).

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664. *Formation of Tyrosine Melanin. Part III.* The Use of Carboxyl-labelled Tyrosine and Dihydroxyphenylalanine in Melanin Formation.*

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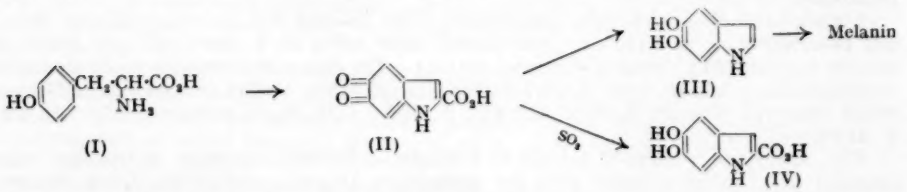
DL-[*carboxy*-^{14}C]-Tyrosine and 3 : 4-dihydroxyphenyl-DL-[*carboxy*-^{14}C]-alanine have been synthesised and used to study melanin formation. It was found that nearly half of the carbon dioxide evolved during the reaction arises from carbon atoms of the amino-acid molecule other than the carboxyl group. Moreover, 2-(3 : 4-dihydroxyphenyl)ethylamine and 5 : 6-dihydroxyindole evolved carbon dioxide during their ærobic conversion into melanin. It was also found that the melanin obtained from the amino-acids retains some of the original carboxyl group.

CURRENT theories concerning the structure of melanin involve polymerisation of indole-5 : 6-quinone. Beer, Clarke, Khorana, and Robertson (*J.*, 1948, 2223) synthesised 5 : 6-dihydroxyindole (III) and 5 : 6-dihydroxyindole-2-carboxylic acid (IV) and found the

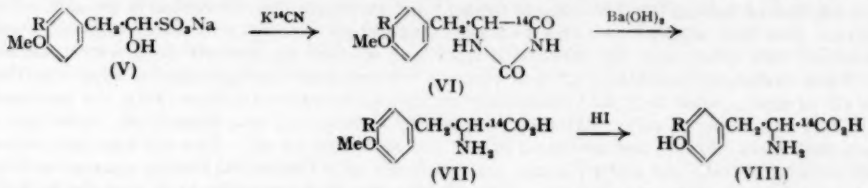


latter, unlike the former, to be stable in alkaline solution. These results imply that tyrosine (I) cyclises and is oxidised to the *o*-quinone (II) which is decarboxylated and

* Part II, *J.*, 1950, 1795.

rearranged to form the indole (III). Raper (*Biochem. J.*, 1927, **21**, 89) prevented decarboxylation by the use of sulphurous acid and so isolated 5 : 6-dimethoxyindole-2-carboxylic acid (cf. IV). Further evidence for this decarboxylation was obtained by Mason (*J. Biol. Chem.*, 1949, **180**, 235) who investigated quantitatively the amount of carbon dioxide evolved during oxidation of 3 : 4-dihydroxyphenylalanine.

We have found that the amount of carbon dioxide evolved during ærobic oxidation of a solution of 3 : 4-dihydroxyphenyl-DL-alanine at pH 8 is equal to, or even greater than, that which could theoretically result from the complete decarboxylation of the amino-acid, but that the yield of melanin is only 60% of the weight of the amino-acid employed.



We have, therefore, prepared DL-[*carboxy*-^{14}C]tyrosine and 3 : 4-dihydroxyphenyl-DL-[*carboxy*-^{14}C]alanine and used these amino-acids to investigate the oxidation. Trial experiments showed that the behaviour of DL-amino-acids in melanin formation was little different from that of their L-forms. In our hands, Loftfield's tyrosine synthesis (*J. Amer. Chem. Soc.*, 1950, **72**, 2499) afforded low yields of an impure product, which could not be purified without considerable loss, and we found it desirable to hydrolyse the intermediate hydantoin (VI; R = H) with barium hydroxide and demethylate the resulting *p*-methoxyphenylalanine (VII; R = H) with concentrated hydrochloric acid. The labelled dihydroxyphenylalanine (VIII; R = OH) was similarly prepared from 3 : 4-dimethoxyphenylacetaldehyde bisulphite compound (V; R = MeO) but the final demethylation was brought about by hydriodic acid. Very pure amino-acids were thus obtained.

Experimental

Combustion of Samples for Isotope Analyses.—Samples (in duplicate) were converted into carbon dioxide by conventional combustion methods. The carbon dioxide was absorbed in barium hydroxide solution, and the barium carbonate separated and washed by centrifugation under ether.

Radioactivity Determinations.—These were carried out on samples of "infinite thickness," approximately 0·2 cm.^{2} in area, with an end-window Geiger counter, the background of which was 9—10 counts/minute. A sample containing 10^{-2} μc of ^{14}C per mg. of substance gave approx. 1300 counts/minute. Sufficient counts to give a standard error of less than 2% were taken; but slight variation in disc size introduced an additional error of ±5%. All values quoted are corrected for background.

Tyrosinase was prepared by the procedure of Mallette, Lewis, Ames, Nelson, and Dawson (*Arch. Biochem.*, 1948, **16**, 283).

5 : 6-Dihydroxyindole was prepared by the method of Beer, Clarke, Khorana, and Robertson (*loc. cit.*).

DL-[carboxy-^{14}C]*Tyrosine.*—A mixture of *p*-methoxyphenylacetaldehyde sodium bisulphite (600 mg.), ammonium carbonate (600 mg.), potassium [^{14}C]cyanide (3·2 mg.; 50 μc), potassium [^{12}C]cyanide (130 mg.), and aqueous ethanol (3 ml.; 50% v/v) was heated in a sealed tube for 4 hours at 100°. The mixture was diluted with water (3 ml.), heated at 105—110° for ½ hour, and cooled overnight. 5-*p*-Methoxybenzylhydantoin was filtered and washed with a little water. This hydantoin (247 mg.), m. p. 175—176°, recrystallised barium hydroxide (5 g.), and water (10 ml.), were refluxed for 8 hours. The warm solution was diluted with water (5 ml.), neutralised to methyl-red with sulphuric acid (6N), cooled, and filtered, the barium sulphate washed with hot water (4 × 10 ml.), and the solution evaporated to 2 ml. under reduced pressure. After 12 hours at 0° the *p*-methoxyphenylalanine was filtered off, washed with alcohol, and dried. This product (190 mg.), m. p. 245—250°, DL-tyrosine (60 mg.), and concentrated hydrochloric acid (2 ml.) were heated together in a sealed tube for 1 hour at 120°. The contents were then diluted with water (7 ml.). The boiling solution was adjusted to pH 6 with ammonium hydroxide

(*d* 0·88), treated with charcoal, filtered, and cooled. The product (140 mg.) was filtered off and recrystallised with carrier DL-tyrosine (40 mg.) from water, yielding DL-[*carboxy*-^{14}C]tyrosine (140 mg.), m. p. 312—315°, specific radioactivity 83 μc/g. (radiochemical yield, 23%) (Found : C, 59·4; H, 6·3. Calc. for $C_9H_{11}O_3N$: C, 59·7; H, 6·1%). A sample was decarboxylated by treatment with ninhydrin (Van Slyke, MacFadyen, and Hamilton, *J. Biol. Chem.*, 1941, **141**, 671) as a check on the distribution of ^{14}C in the molecule and the reliability of the combustion procedure (see Table 1). We were, however, unable to apply this method to 3 : 4-dihydroxyphenylalanine.

3 : 4-*Dihydroxyphenyl*-DL-[carboxy-^{14}C]*alanine*.—A solution of ethyl chloroacetate (37 g.), veratraldehyde (50 g.), and anhydrous ether (70 ml.) was added, during 1 hour with stirring, to a solution of sodium (7 g.) in ethanol (50 ml.) and methanol (50 ml.) cooled in ice–salt. The mixture was then allowed to warm to room temperature, poured into water (650 ml.), and extracted with ether, and the ethereal extract was washed successively with water, sodium hydrogen carbonate solution (3%), and water. The solution was then diluted with a further 400 ml. of ether, cooled to 5°, and poured into an ice-cold solution of sodium (6·9 g.) in methanol (100 ml.) and water (6 ml.). After 10 minutes the sodium salt was filtered off, made into a paste with ether (30 ml.) and methanol (6 ml.) and again filtered off. The salt was then mixed with ethanol (20 ml.) and water (15 ml.) and gradually added to stirred boiling aqueous sodium hydrogen sulphite (250 ml.; *d* 1·29). The solution was kept overnight at 0° and the 3 : 4-dimethoxyphenylacetaldehyde bisulphite compound (40 g.) then filtered off. A mixture of the above (600 mg.), ammonium carbonate (600 mg.), potassium [^{14}C]cyanide (2·6 mg.; 41 μc), potassium [^{12}C]cyanide (130 mg.), and aqueous ethanol (3 ml.; 50%) was heated in a sealed tube for 4 hours at 100°. The hydantoin (VI; R = OMe) (250 mg.), m. p. 156—160°, isolated as above, was refluxed for 8 hours with recrystallised barium hydroxide (8 g.) and water (10 ml.). The warm solution was diluted with water (5 ml.), neutralised to methyl-red with sulphuric acid (6N), cooled, and filtered, the precipitate washed with hot water (4 × 10 ml.), and the solution evaporated to 2 ml. Ethanol (5 ml.) was then added and the solution kept for 12 hours at 0°. 3 : 4-Dimethoxyphenyl[*carboxy*-^{14}C]alanine was filtered off, washed with ethanol, and dried. The product (160 mg.), m. p. 240—245°, 3 : 4-dihydroxy-DL-phenylalanine (60 mg.), redistilled hydriodic acid (2·5 ml.), and red phosphorus (10 mg.) were heated in an evacuated Pyrex tube for 1 hour at 110°. The contents were filtered, the phosphorus washed with water, and the resulting solution evaporated to dryness under reduced pressure (nitrogen). The residue was dissolved in water (3 ml.), and the solution adjusted to pH 6 with ammonia (*d* 0·88) and evaporated to dryness. The residue was then dissolved in water (3 ml.) and diluted with ethanol (20 ml.), and the solution was distilled under reduced pressure in an atmosphere of nitrogen until precipitation occurred, whereupon it was cooled at 0° for 1 hour, and filtered. This procedure was repeated until no more 3 : 4-dihydroxyphenylalanine was obtained. This amino-acid (124 mg.), together with carrier 3 : 4-dihydroxyphenyl-DL-alanine (80 mg.), was recrystallised from water (3 ml.) saturated with sulphur dioxide (charcoal), to give the product (103 mg.), m. p. 286—288°, specific radioactivity 33 μc/g. (radiochemical yield, 8·5%) (Found : C, 54·3; H, 6·0. Calc. for $C_9H_{11}O_4N$: C, 54·8; H, 5·8%).

2-(3 : 4-*Dihydroxyphenyl*)*ethylamine Hydrochloride*.—3 : 4-Dimethoxyphenylethylamine (1 g.) (Bide and Wilkinson, *Chem. and Ind.*, 1945, **64**, 89) and concentrated hydrochloric acid (8 ml.) were heated for 2 hours at 140—160°. The whole was taken to dryness, the residue dissolved in a minimum amount of warm ethanol, and ether was added until the hydrochloride was precipitated. The solution was cooled and filtered and the 2-(3 : 4-dihydroxyphenyl)ethylamine hydrochloride recrystallised from hydrochloric acid (1 : 1) (yield, 0·5 g.; m. p. 247°) (Found : C, 50·5; H, 6·2. Calc. for $C_8H_{12}O_2NCl$: C, 50·7; H, 6·3%).

Oxidation Procedure.—A slow stream of carbon dioxide-free oxygen was passed first through a test bottle containing barium hydroxide and then into a two-necked flask, immersed in a thermostat at 20° and containing freshly boiled distilled water (10 ml.) and phosphate buffer solution of pH 8 [in the tyrosine experiment dihydroxyphenylalanine (5 ml.), dihydroxyindole (15 ml.) and dihydroxyphenylethylamine hydrochloride (30 ml.) were used]. A solution (1 ml.) of tyrosinase was also added in the tyrosine experiment. The flask was equipped with dropping funnel and inlet and outlet tubes. The oxygen was then passed through a series of four bubblers, the first three empty and the fourth containing 2N-sodium hydroxide.

The apparatus was swept out for 4 hours. Carbon dioxide-free sodium hydroxide solution (1·5 and 0·5 ml. respectively) was then placed in the second and third bubblers, and a solution of the compound under test in carbon dioxide-free distilled water (for tyrosine, 90 ml.; for dihydroxyphenylalanine, dihydroxyindole, and dihydroxyphenylethylamine hydrochloride,

50 ml.) added from the dropping funnel. The experiment was continued for 3 days with an oxygen flow of approx. 25 bubbles (1·2 c.c.) per minute. The melanin was then completely precipitated by 2N-hydrochloric acid (4 ml.), and the apparatus swept out with oxygen for a further 4 hours. The absorption tubes were washed out with carbon dioxide-free water, and the alkaline solution protected from the atmosphere with a layer of ether and treated with 4N-ammonium chloride (0·25 ml.), excess of barium hydroxide added, and the precipitated barium carbonate centrifuged off and, after one washing with saturated barium chloride solution and two with carbon dioxide-free water, dried at 140° for 1½ hours and weighed (radioactive experiments showed that not more than about 1% of the carbon dioxide escaped absorption). The melanin was centrifuged, washed three times with water, and dried to constant weight over concentrated sulphuric acid *in vacuo*, and the melanin (except the sample analysed) was then refluxed for 24 hours with hydrochloric acid (2N), and then water, as described by Raper and Wormall (*Biochem. J.*, 1925, **19**, 90), then centrifuged and washed, and a further sample analysed. The procedure was once more repeated. The weights of melanin quoted in Tables 1 and 2 are corrected for any inorganic

TABLE 1.

Compound	Weight (mg.)	Radioactivity (as $Ba^{14}CO_3$) (counts/min.)
Tyrosine	59·8	353
$BaCO_3$ resulting from melanin formation	41·0	1730
$BaCO_3$ formed by action of ninhydrin on tyrosine	—	3004
Melanin	21·0	57
Melanin (refluxed for 24 hrs. with 2N-HCl)	—	23
Melanin (refluxed for 48 hrs. with 2N-HCl)	—	19
Water-soluble residues (containing 20% of C)	92·0	395

$$\frac{Ba^{14}CO_3 \text{ from melanin formation}}{Ba^{14}CO_3 \text{ from combustion of tyrosine}} = 4{\cdot}9$$

TABLE 2.

Compound	Weight (mg.)	Radioactivity (as $Ba^{14}CO_3$) (counts/min.)
Dihydroxyphenylalanine	62·5	475
$BaCO_3$ resulting from melanin formation	68·0	2410
Melanin	37·4	83
Melanin (refluxed 24 hrs. with 2N-HCl	—	61
Melanin (refluxed 48 hrs. with 2N-HCl)	—	15
Water soluble residues (containing 4% of C)	100	260

$$\frac{Ba^{14}CO_3 \text{ from melanin formation}}{Ba^{14}CO_3 \text{ from combustion of dihydroxyphenylalanine}} = 5{\cdot}1.$$

residue (less than 3%), and the weights of barium carbonate evolved in melanin formation corrected for any extraneous barium carbonate (less than 2%).

The liquors obtained from centrifuging the melanin were evaporated to dryness, dried to constant weight *in vacuo* over concentrated sulphuric acid, and analysed for carbon, and 20 mg. were burnt for isotope analysis.

If the evolved carbon dioxide arose from the carboxyl group of the amino-acid, then the ratios given in the Tables should both be 9. It is therefore clear that nearly half of this carbon dioxide (subsequently referred to as " non-carboxyl carbon dioxide ") arises from one or more of the other eight carbon atoms of the amino-acid molecule. This was further substantiated by the ærobic oxidation of the carboxyl-free 2-(3 : 4-dihydroxyphenyl)ethylamine and 5 : 6-dihydroxyindole at pH 8, both of which led to the production of melanin with the evolution of carbon dioxide (Table 3).

TABLE 3.

	2-(3 : 4-Dihydroxyphenyl)-ethylamine	5 : 6-Dihydroxy-indole
Compound (mg.)	80·0	47·0
$BaCO_3$ resulting from melanin formation (mg.)	21·3	30·5
Melanin (mg.)	31·2	43·0

At present we have no proof that the amino-acid, dihydroxyphenylethylamine, or dihydroxyindole residues which evolve this non-carboxyl carbon dioxide are in fact incorporated into the melanin molecule. It may, however, be significant that the amounts of carbon dioxide evolved by dihydroxyindole, and the amounts of non-carboxyl carbon dioxide evolved by the two amino-

acids, appear to bear some relation to the weight of melanin produced. If it should emerge that this non-carboxyl carbon dioxide is really evolved from residues which are incorporated into the melanin, then a ring contraction or a ring fission would be implied. The oxidative fission theory (*loc. cit.*) was rejected on the basis that hydroxylamine did not prevet pigment formation. Later work has shown that a higher concentration of hydroxylamine does inhibit pigment formation. Perhaps, however, our results mean simply that a small proportion of the amino-acid is being oxidised completely to carbon dioxide. We are therefore now attempting to settle this point by synthesis of the amino-acids or (preferably) the dihydroxyphenylethylamine labelled at specific positions in the benzene nucleus and at the α- or β-position of the side chain, for use in a further study of melanin formation. One can picture the ring contraction occuring by a benzilic acid type of rearrangement (*e.g.*, on the quinone derived from 5 : 6-dihydroxyindole) or by oxidative fission (Clemo and Duxbury, *J.*, 1950, 1795).

It is also interesting that some of the carboxyl groups are apparently retained in the melanin (either combined in the molecule or adsorbed as amino-acid). This should be borne in mind when considering analytical data on melanins prepared from amino-acids.

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KING'S COLLEGE, NEWCASTLE-ON-TYNE, 2. [*Received, June 6th*, 1952.]

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665. *Ionisation of Tri-p-tolylmethyl Chloride in Nitroalkanes.*

By A. BENTLEY and ALWYN G. EVANS.

A study has been made of the thermodynamics of the equilibrium $(p\text{-}C_6H_4Me)_3CCl_{(s)} \rightleftharpoons (p\text{-}C_6H_4Me)_3C^+Cl^-_{(s)}$ in nitromethane, nitroethane, and 2-nitropropane. The values of the equilibrium constant, and of $\Delta G°$, $\Delta H°$, and $\Delta S°$ for the forward reaction have been obtained in these three solvents. The effect of change of solvent on the $\Delta G°$, $\Delta H°$, and $\Delta S°$ values is discussed, and the results for $(p\text{-}C_6H_4Me)_3CCl$ are compared with those obtained earlier for Ph_3CCl.

BENTLEY, A. G. EVANS, and HALPERN recently (*Trans. Faraday Soc.*, 1951, **47**, 711) described a method for obtaining $\Delta G°$, $\Delta H°$, and $\Delta S°$ for the ionisation of triphenylmethyl chloride in nitroalkanes. In the present work we give the corresponding results for the ionisation of tri-*p*-tolylmethyl chloride in nitroalkanes. As discussed for the earlier case, the following conditions must be fulfilled in order that this method may be used.

(*a*) The carbonium ion R^+ must not react with the solvent. It was originally shown by Hantzsch (*Z. physikal. Chem.*, 1909, **65**, 41) that when nitromethane was dissolved in concentrated sulphuric acid the solution showed the normal depression of the freezing point. This indicated that nitromethane did not accept protons from the acid to any appreciable extent. It has been shown recently by Gillespie (*J.*, 1950, 2541) that nitromethane is ionised in 100% sulphuric acid to an extent which would correspond to about 21% at 0·1 molal concentration. This indicates that nitromethane is very slightly basic, and the question of its acceptance of R^+ ions in the solution we are using must therefore be considered. If the nitroalkane accepts the R^+ ion (as it does the proton to a small extent in concentrated sulphuric acid), giving the $(CH_3{\cdot}NO_2R)^+_{(s)}$ ion, the spectrum of this ion would be very different from that of the $R^+_{(s)}$ ion produced from ROH in concentrated sulphuric acid, where the presence of the $R^+_{(s)}$ ion has been established by freezing-point measurements for the case when R is Ph_3C (Hantzsch, *Z. physikal. Chem.*, 1908, **61**, 257; Hammett and Deyrup, *J. Amer. Chem. Soc.*, 1933, **55**, 1600). The fact that we find the spectrum of RCl in nitromethane to be almost identical in shape with that of ROH in concentrated sulphuric acid establishes that what we are measuring spectrophotometrically is in fact the concentration of $R^+_{(s)}$ ions. If there were any interaction between R^+ and nitroalkane to give an ion of the type $(CH_3{\cdot}NO_2R)^+_{(s)}$, then under our conditions, where the concentration of R^+ is extremely small ($\simeq 10^{-5}$ molal), its concentration would be negligible; in any case, it would not be included in our spectroscopically determined $R^+_{(s)}$

concentration, and so would not affect the validity of our equilibrium constant, $K = [R^+Cl^-_{(s)}]/[RCl]$.

(*b*) The R^+ ion must not rearrange or form an olefin by loss of a proton. This condition is fulfilled for the tri-*p*-tolylmethyl ion.

(*c*) The polarity of the nitroalkane solvents and the stability of the R^+ ions must be such as to give a measurable equilibrium concentration of R^+ ions at ordinary temperatures. This was found to be the case.

The effect of concentration, temperature and change of solvent on the equilibrium constant was determined for the reaction :

$$(p\text{-}CH_3\cdot C_6H_4)_3CCl_{(s)} \rightleftarrows (p\text{-}CH_3\cdot C_6H_4)_3C^+Cl^-_{(s)} \quad . \quad . \quad . \quad . \quad (1)$$

Experimental

Materials.—Tri-*p*-tolylmethyl chloride was a product of Mersey Chemicals Ltd. When received it had a good colour and m. p., and so a quantitative determination of the spectrum was made over the range 360—480 mμ, in nitromethane. A small amount of the chloride was then recrystallised from light petroleum, and the spectrum and m. p. were found to be unchanged. The measurements were therefore made on the material as received from Mersey Chemicals (m. p. 171°).

Tri-*p*-tolylmethyl alcohol was prepared by hydrolysis of the chloride. The chloride was dissolved in concentrated sulphuric acid and poured into ice-water. The alcohol was recrystallised from aqueous ethanol and had m. p. 93°.

Concentrated sulphuric acid was analytical-grade material from J. W. Towers Ltd.

Nitromethane and nitroethane were Light's products. The 2-nitropropane was kindly given by Imperial Chemical Industries Limited, Billingham Division. All the nitroalkanes were dried over phosphoric oxide and distilled under reduced pressure. B. p.s were 100·5°, 115°, and 121° respectively.

Procedure.—The dependence of optical density *D* on wave-length for tri-*p*-tolylmethyl chloride in each of the nitroalkanes and for the alcohol in 98% sulphuric acid was measured by a Unicam Spectrophotometer, and the results are shown in Figs. 1*a*, *b*, and *c*. The spectra of the chloride in the three nitroalkanes are seen to be very similar to that of the alcohol in concentrated sulphuric acid. The dependence of optical density on concentration of the chloride was measured (*a*) on a Spekker photometer with a filter with maximum transmission at wave-length 440 mμ, (*b*) on a photomultiplier with an Ilford 601 filter with maximum transmission in the region 400—460 mμ, and (*c*) on the Unicam spectrophotometer at wave-length 450 mμ.

The dependence of optical density on chloride concentration is shown in Figs. 2*a*, *b*, and *c*. It is seen that the optical densities measured on the Spekker photometer, and on the photomultiplier are directly proportional to those measured at wave-length 450 mμ on the Unicam instrument, and so the optical density obtained by the Spekker photometer and by the photomultiplier was taken as a measure of the carbonium ion concentration.

The dependence of optical density on temperature was measured by the photomultiplier. A new apparatus was designed for the temperature control of the cell liquid. This apparatus consisted of a metal box fitted with a heater, mercury–toluene regulator, stirrer, thermometer, and " Perspex " windows to allow passage of light. The entire box was surrounded by a wooden outer jacket to act as lagging. Two Beckman cells were used. One was filled with solvent, the other with solution; these were water-proofed and completely immersed in the bath. The cell carriage was moved by means of a rack and pinion. In this way there was no danger of temperature gradients within the cell, and temperatures are accurate to ±0·1°.

Results

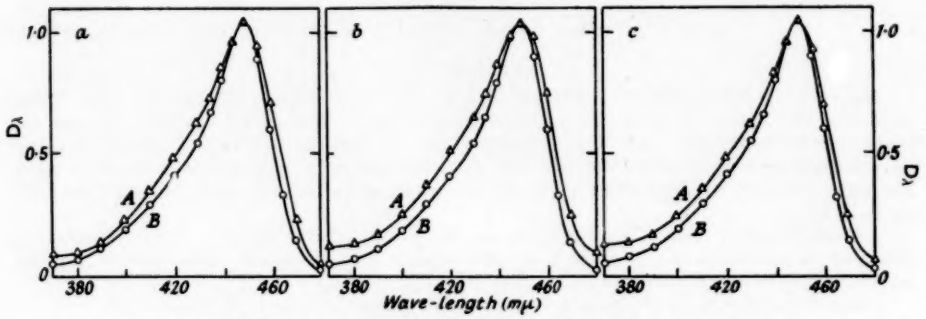
The shape of the absorption spectrum obtained for tri-*p*-tolylmethyl alcohol in 98% sulphuric acid (Figs. 1*a*, *b*, and *c*) is similar to that obtained previously by Newman and Deno (*J. Amer. Chem. Soc.*, 1951, **73**, 3644), who also showed by cryoscopic measurements that the reaction

$$(p\text{-}CH_3\cdot C_6H_4)_3C\cdot OH + 2H_2SO_4 \longrightarrow (p\text{-}CH_3\cdot C_6H_4)_3C^+ + 2HSO_4^- + H_3O^+ \quad . \quad (2)$$

goes to completion. On the basis of the completeness of reaction (2), our sulphuric acid solution containing $1{\cdot}195 \times 10^{-5}$ mole/l. of tri-*p*-tolylmethyl alcohol has a concentration of

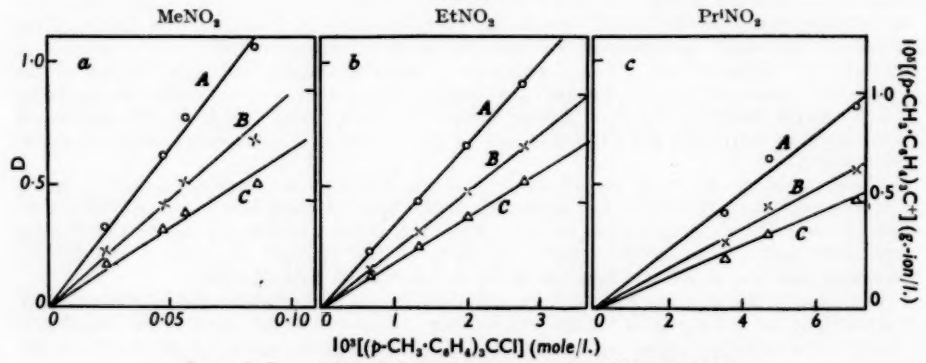
(p-$CH_3 \cdot C_6H_4)_3C^+$ ions of $1 \cdot 195 \times 10^{-5}$ g.-ion/l. The spectra of tri-p-tolylmethyl chloride in nitromethane ($8 \cdot 63 \times 10^{-5}$ mole/l.), in nitroethane ($3 \cdot 1 \times 10^{-3}$ mole/l.), and in 2-nitropropane ($9 \cdot 05 \times 10^{-3}$ mole/l.) are shown in Figs. 1*a*, *b*, and *c*. These curves are calculated from results at other concentrations (by using the observed direct proportionality between optical density and the concentration of the chloride shown in Figs. 2), so that they coincide at 450 mμ with the curve for a solution of the alcohol in concentrated sulphuric acid of a concentration $1 \cdot 195 \times 10^{-5}$ mole/l.

FIG. 1.



Curve A (FIG. 1*a*), (p-$CH_3 \cdot C_6H_4)_3CCl$ *in* $MeNO_2$, $8 \cdot 63 \times 10^{-5}$ *mole/l.*
Curve A (FIG. 1*b*), (p-$CH_3 \cdot C_6H_4)_3CCl$ *in* $EtNO_2$, $3 \cdot 10 \times 10^{-3}$ *mole/l.*
Curve A (FIG. 1*c*), (p-$CH_3 \cdot C_6H_4)_3CCl$ *in* Pr^iNO_2, $9 \cdot 05 \times 10^{-3}$ *mole/l.*
Curve B, (p-$CH_3 \cdot C_6H_4)_3C \cdot OH$ *in* 98% H_2SO_4, $1 \cdot 195 \times 10^{-5}$ *mole-l.*

FIG. 2.



Curve A, D_{450} *and* [(p-$CH_3 \cdot C_6H_4)_3C^+$] *against* [p-$CH_3 \cdot C_6H_4)_3CCl$].
Curve B, D (*Photomultiplier*) *against* [(p-$CH_3 \cdot C_6H_4)_3CCl$].
Curve C, D (*Spekker*) *against* [(p-$CH_3 \cdot C_6H_4)_3CCl$].

These results establish that the spectrum which we measure in the nitroalkanes is that due to (p-$CH_3 \cdot C_6H_4)_3C^+$ ion produced by ionisation of the chloride (a solution of the chloride has no absorption in this region when dissolved in a non-polar solvent). Further, in view of the close similarity of these spectra we assume that the extinction coefficient of p-$CH_3 \cdot C_6H_4)_3C^+$ is the same in the three nitroalkanes as it is in concentrated sulphuric acid (in this respect tri-p-tolylmethyl chloride differs from triphenylmethyl chloride, the spectrum for which broadens appreciably from nitromethane to nitroethane to 2-nitropropane; Bentley, A. G. Evans, and Halpern, *loc. cit.*). Thus those solutions of tri-p-tolylmethyl chloride in nitroalkanes, for which the spectra are shown in Figs. 1*a*, *b*, and *c*, will each have a concentration of (p-$CH_3 \cdot C_6H_4)_3C^+$ ions of $1 \cdot 195 \times 10^{-5}$ g.-ion/l.

Nature of the Equilibrium.—To find the nature of the equilibrium obtaining in these

solutions of tri-*p*-tolylmethyl chloride in nitroalkanes, the same procedure was employed for each of the nitroalkane solvents as was used for the earlier experiments on triphenylmethyl chloride in nitromethane. The concentration of $(p\text{-}CH_3\cdot C_6H_4)_3C^+$ ions was measured for different total concentrations of the chloride. A set of typical results are shown in Figs. 2*a*, *b* and *c*. In each case curve *A* shows the absorption at 450 mμ (as measured on the Unicam spectrophotometer) and the $(p\text{-}CH_3\cdot C_6H_4)_3C^+$ concentration (calculated as above), plotted against the concentration of the chloride. In the case of tri-*p*-tolylmethyl chloride in nitromethane the concentration of un-ionised chloride is less than that of the total concentration of chloride and this has been allowed for, but in the solvents nitroethane and 2-nitropropane the ion concentration is so small that the concentration of un-ionised chloride has been taken as equal to the total concentration of chloride in solution. Curves *B* and *C* show the absorption of the same solutions, measured on the photomultiplier and on the Spekker photometer. A good linear relation is obtained between optical density and chloride concentration in each nitroalkane, and for each method of measurement.

The direct proportionality between the concentrations of $(p\text{-}CH_3\cdot C_6H_4)_3C^+$ and $(p\text{-}CH_3\cdot C_6H_4)_3CCl$ establishes that the equilibrium

$$(p\text{-}CH_3\cdot C_6H_4)_3CCl_{(s)} \rightleftarrows (p\text{-}CH_3\cdot C_6H_4)_3C^+Cl^-_{(s)} \quad . \quad . \quad . \quad (3)$$

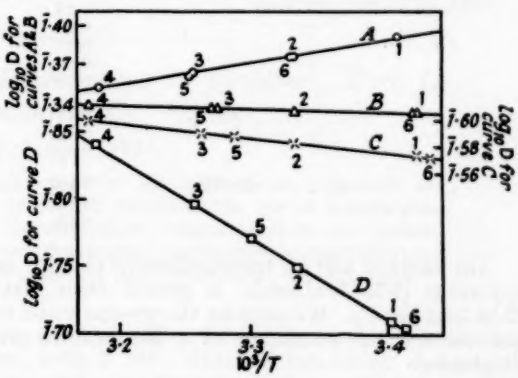


FIG. 3.

Curve A, $(p\text{-}CH_3\cdot C_6H_4)_3CCl$ *in* $MeNO_2$.
Curve B, $(p\text{-}CH_3\cdot C_6H_4)_3CCl$ *in* $EtNO_2$.
Curve C, $(p\text{-}CH_3C_6H_4)_3CCl$ *in* Pr^iNO_2.
Curve D, $(C_6H_5)_3CCl$ *in* $MeNO_2$.

exists over the range of concentration studied. Any dissociation of the ion pairs would cause a deviation from this direct proportionality relationship. Values of *K* defined by

$$K = [(p\text{-}CH_3\cdot C_6H_4)_3C^+Cl^-_{(s)}]/[(p\text{-}CH_3\cdot C_6H_4)_3CCl_{(s)}]$$

were obtained from the slopes of the curves *A*, and these are given in the annexed Table, together with the values of ΔG° calculated from *K*. We estimate the accuracy of ΔG° to be within the limits $\pm 0{\cdot}17$ kcal./mole.

Solvent	Temp.	*K*	ΔG° (kcal./mole)
$MeNO_2$	16°	$1{\cdot}71 \times 10^{-1}$	1·0
$EtNO_2$	17	$3{\cdot}85 \times 10^{-2}$	3·2
Pr^iNO_2	17	$1{\cdot}33 \times 10^{-2}$	3·8

Dependence of K *on Temperature.*—The $(p\text{-}CH_3\cdot C_6H_4)_3C^+$ concentration of a solution of tri-*p*-tolylmethyl chloride in nitroalkane was measured at different temperatures as described earlier, the same solution being used at all temperatures. The same experiment was done with triphenylmethyl chloride in order to repeat the earlier experiments with the new apparatus. A set of typical plots for tri-*p*-tolylmethyl chloride in nitromethane, nitroethane, and 2-nitropropane, and for triphenylmethyl chloride in nitromethane are shown in Fig. 3, curves *A*, *B*, *C*, and *D* respectively. The points in Fig. 3 are numbered to show the sequence in which the temperature of the solution was varied. The plots are for log *D* against $1/T$, as it is not necessary to plot log *K* in order to obtain ΔH°. The

change in concentration of carbonium ions due to expansion of the solvent has been allowed for in each of these plots (in the case of nitromethane the change of density with temperature was known. For nitroethane and 2-nitropropane the required volume change was determined by dilatometer experiments). As in our earlier paper we have again assumed that the extinction coefficient, ε, is independent of temperature. The values of ΔH° were obtained from the slopes of these lines, and by combination of these values with ΔG°, values of ΔS° were obtained. The value of ΔG° for triphenylmethyl chloride is $4{\cdot}46 \pm 0{\cdot}17$ kcal./mole at 16° (Bentley, A. G. Evans, and Halpern, *loc. cit.*). The results are given in the annexed Table. We consider the ΔH° (av.) and the ΔS° values to be accurate to $\pm 0{\cdot}2$ kcal./mole and $\pm 1{\cdot}3$ cal./mole deg., respectively.

Solute	Solvent	ΔH° (exp.) (kcal./mole)	ΔH° (av.) (kcal./mole)	ΔS° (cal./mole deg.)	
Ph_3CCl	$MeNO_2$	2·68 2·72 2·85	2·75	− 5·9	at 16°
$(p\text{-}CH_3\cdot C_6H_4)_3CCl$	$MeNO_2$	−0·73 −0·72 −0·62 −0·69 −0·58 −0·58 −0·59 −0·70 −0·60 −0·71	−0·65	− 5·7	at 16°
,, ...	$EtNO_2$	0·131 0·101 0·150	0·13	−10·6	at 17°
,, ...	Pr^iNO_2	0·507 0·63 0·65	0·60	−11·0	at 17°

The value of ΔH° for triphenylmethyl chloride in nitromethane obtained with the new apparatus (2·75 kcal./mole) is greater than that obtained by our earlier technique (2·35 kcal./mole). We consider the present value to be the more accurate because in the new method the possibility of a temperature gradient in the cell solution has been eliminated.

Discussion

Change of Solvent.—The results in the second Table show that as the solvent changes from nitromethane to nitroethane to 2-nitropropane the ionisation of tri-*p*-tolylmethyl chloride becomes progressively less exothermic. This is to be expected for an ionisation reaction of this type [reaction (3)], since the dielectric constant of the solvent decreases along this sequence. [The dielectric constant is 39 for nitromethane and 30 for nitroethane (Intern. Crit. Tables, Vol. 6, pp. 83, 85). The value for 2-nitropropane is not known, but is very probably still smaller.]

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The change in ΔH° from triphenyl- to tri-*p*-tolylmethyl chloride is such that the ionisation of the latter is 3·4 kcal./mole more exothermic than that of the former (this difference of ΔH° was obtained using the same batch of solvent for each chloride). We hope to find out whether or not the effect of the *p*-methyl groups is additive by examining phenyldi-*p*-tolylmethyl chloride.

Shape of the Spectrum of R^+.—The introduction of three *p*-methyl groups into triphenylmethyl chloride produces a marked change in the spectrum of the carbonium ion. The two peaks at 410 and 430 mμ for the Ph_3C^+ ion are replaced by a single peak of more than twice the intensity at 450 mμ. We attribute this new peak to the presence of the $>\overset{+}{C}\cdot C_6H_4\cdot CH_3$ group, and the absence of the 410 and 430 mμ peaks to the absence of the $>\overset{+}{C}Ph$ group. This is confirmed by preliminary results for phenyldi-*p*-tolylmethyl chloride.

We thank the D.S.I.R. for a Junior Grant to one of us (A. B.)

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666. *Electrochemical Measurements in Pyridine. Part I. The System* Cu–Cu^+–Cu^{++}.

By A. K. GUPTA.

A technique for the measurement of electrochemical potentials in anhydrous pyridine has been developed, including the use of a hydrogen electrode as arbitrary zero. Thermodynamic relationships in the system Cu–Cu^+–Cu^{++} in pyridine have been determined, and it has been shown that, in contrast to the state of affairs in water, the equilibrium $2Cu^+ \rightleftharpoons Cu + Cu^{++}$ favours Cu^+ very strongly.

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EXPERIMENTAL

Materials.—Unless otherwise stated, analytical-reagent quality anhydrous materials were used without further treatment. Crude pyridine, b. p. 115—120°, was refluxed for several hours with some 5% of ferric chloride, to destroy oxidizable impurities. It was then fractionated in a 2-ft. column of the Widmer type with stainless-steel gauze packing, moisture being excluded during distillation by calcium chloride drying tubes. A fraction boiling over a 0·1° range around 115·5°/750 mm. was collected and stored over potassium hydroxide flake. No special precautions were taken to exclude water when handling this purified pyridine, other than exposing it to the air for the shortest possible time, but it was shown to remain satisfactorily dry and to contain less than 0·01% of water.

Cuprous chloride was prepared by reducing an equimolecular aqueous solution of copper sulphate and sodium chloride by sulphur dioxide. It was dried and stored *in vacuo*, and under these conditions remained white for many weeks. Its solutions in pyridine were dark brown,

change in concentration of carbonium ions due to expansion of the solvent has been allowed for in each of these plots (in the case of nitromethane the change of density with temperature was known. For nitroethane and 2-nitropropane the required volume change was determined by dilatometer experiments). As in our earlier paper we have again assumed that the extinction coefficient, ε, is independent of temperature. The values of ΔH° were obtained from the slopes of these lines, and by combination of these values with ΔG°, values of ΔS° were obtained. The value of ΔG° for triphenylmethyl chloride is $4{\cdot}46 \pm 0{\cdot}17$ kcal./mole at 16° (Bentley, A. G. Evans, and Halpern, *loc. cit.*). The results are given in the annexed Table. We consider the ΔH° (av.) and the ΔS° values to be accurate to $\pm 0{\cdot}2$ kcal./mole and $\pm 1{\cdot}3$ cal./mole deg., respectively.

Solute	Solvent	ΔH° (exp.) (kcal./mole)	ΔH° (av.) (kcal./mole)	ΔS° (cal./mole deg.)	
Ph_3CCl	$MeNO_2$	2·68 2·72 2·85	2·75	− 5·9	at 16°
$(p\text{-}CH_3\cdot C_6H_4)_3CCl$	$MeNO_2$	−0·73 −0·72 −0·62 −0·69 −0·58 −0·58 −0·59 −0·70 −0·60 −0·71	−0·65	− 5·7	at 16°
,, ...	$EtNO_2$	0·131 0·101 0·150	0·13	−10·6	at 17°
,, ...	Pr^iNO_2	0·507 0·63 0·65	0·60	−11·0	at 17°

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Materials.—Unless otherwise stated, analytical-reagent quality anhydrous materials were used without further treatment. Crude pyridine, b. p. 115—120°, was refluxed for several hours with some 5% of ferric chloride, to destroy oxidizable impurities. It was then fractionated in a 2-ft. column of the Widmer type with stainless-steel gauze packing, moisture being excluded during distillation by calcium chloride drying tubes. A fraction boiling over a 0·1° range around 115·5°/750 mm. was collected and stored over potassium hydroxide flake. No special precautions were taken to exclude water when handling this purified pyridine, other than exposing it to the air for the shortest possible time, but it was shown to remain satisfactorily dry and to contain less than 0·01% of water.

Cuprous chloride was prepared by reducing an equimolecular aqueous solution of copper sulphate and sodium chloride by sulphur dioxide. It was dried and stored *in vacuo*, and under these conditions remained white for many weeks. Its solutions in pyridine were dark brown,

the solid in contact with saturated solutions being almost black. Anhydrous cupric chloride (B.D.H.) was used, and was stored *in vacuo*. Lithium chloride was dried at 120° and stored *in vacuo*.

Oxygen-free nitrogen was obtained by bubbling gas from a cylinder through a total depth of about 4 feet of a solution of alkaline dithionite (160 g./l. of sodium " hydrosulphite," 150 g./l. of sodium hydroxide, and 8 g./l. of sodium anthraquinone-β-sulphonate) to remove most of the oxygen, drying it with concentrated sulphuric acid and phosphoric oxide, and finally freeing it from oxygen with one or more bubblers containing copper powder and a saturated solution of cuprous chloride in pyridine; as discussed below, this last system has a great affinity for oxygen. All-glass connections were necessary from the first cuprous chloride bubbler onwards.

Apparatus.—Conventional all-glass potentiometric cells were used, fitted with ground sockets for the reference electrode, burettes, etc. Platinum electrodes were of foil about 1 cm. square; they were cleaned in chromic acid, washed with distilled water, and dried at 120° before use. Silver electrodes were made by electroplating platinum electrodes, an aqueous solution of potassium argentocyanide being used. They were washed with water and pyridine and dried at 120°. Copper electrodes were made either from copper foil or by electroplating platinum electrodes from aqueous copper sulphate containing a little alcohol. They were washed first with water, then with pyridine, and were kept under pyridine. No difference in potential was detected between the foil and the plated electrodes.

All the pyridine solutions used were very poor conductors of electricity, and it was consequently necessary to shield all leads carefully and to use a potentiometer with a very high input resistance, such as a Marconi or Cambridge pH meter, allowing readings to $\pm\frac{1}{2}$ mv. Another consequence of the high cell resistances was that an oil thermostat was necessary at temperatures above 18°; erratic results were obtained in a water thermostat, apparently because the water provided a leakage path of resistance comparable with that of the cell itself.

Reference Electrodes.—(i) *Hydrogen electrode in pyridine.* A few experiments were made to explore the possibility of setting up in pyridine a reversible hydrogen electrode of the type established in water. A platinum foil electrode of about 2 sq. cm. surface area was platinized in the usual way in water, then washed well with pyridine and kept under it when not in use. This electrode was immersed in pyridine solutions of pyridine hydrochloride of various concentrations between 0·001 and 0·055M, prepared by absorbing dry hydrogen chloride in anhydrous pyridine. Hydrogen from a cylinder, purified as described for nitrogen, was bubbled through the solutions, and the potential of the platinized electrode was measured relative to the silver–silver nitrate electrode discussed below. It was found essential to use freshly-platinized electrodes, as their efficiency fell rapidly with time. Separate experiments showed that no detectable hydrogenation of the pyridine occurred under these conditions.

The results obtained at 18° and 739 mm. pressure fitted the equation

$$E = E^\circ(H_2, H^+) + 51 \log_{10}[HCl]$$

which compares reasonably well with the theoretical equation

$$E = E^\circ\ (H_2, H^+) + 58 \log_{10} a_h$$

where a_h is the hydrogen-ion activity in the solution. As [HCl] $\longrightarrow$ 0, so presumably does $a_h \longrightarrow [H^+] \longrightarrow$ [HCl]; therefore, using the value of E obtained at the lowest [HCl], and the theoretical factor of 58, we have:

$E^\circ\ (H_2, H^+) = -534$ mv relative to $Ag|AgNO_3$, 0·048M at 18° and 739 mm.

However, although it appeared that a hydrogen electrode of the Hildebrandt type did function approximately reversibly in pyridine, it was not such a convenient reference electrode for frequent use as a metal–metal ion one.

(ii) *Silver–silver nitrate electrode.* The instability in pyridine of mercurous salts rules out the use of a calomel electrode in that solvent, and previous workers (*e.g.*, Abegg and Neustadt, *loc. cit.*) have found the $Ag|AgNO_3$ in pyridine electrode to be the most stable and reproducible of a number of metal electrodes. Sakhanov and Grunbaum (*J. Russ. Phys. Chem. Soc.*, **1916**, **48**, 1794) found that the potentials of concentration cells of the type

$$Ag|AgNO_3|_{c_1}\ \ AgNO_3|_{c_2}Ag$$

obeyed the equation $E = (RT/F)\ln c_1/c_2$ at low concentrations. This was confirmed in the present work, a straight line of slope 53 (theoretical 56·8) being obtained by plotting E (at 12°) against $\log_{10} c_1/c_2$ over the concentration range 0·002—0·05M.

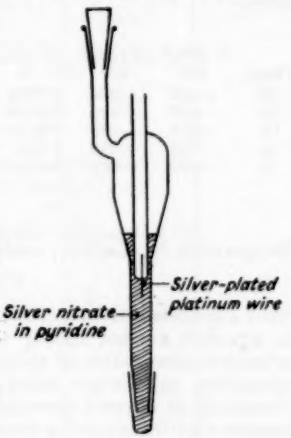
The $Ag|AgNO_3$ half-cell was therefore chosen as a reference electrode, a (purely arbitrary) silver nitrate concentration of 0·048M being used throughout. The form of half-cell used is shown in Fig. 1, contact between the silver nitrate solution inside and the main solution being made by diffusion past the ungreased cap on the reference electrode.

To assess the possibility of reducing the liquid-junction potential by adding a second electrolyte to the reference electrode, the E.M.F. of the cell

$$\underset{E_1}{Ag|AgNO_3,0{\cdot}048\text{M}} \underset{E_2}{|MCl|} \underset{E_3}{AgNO_3,0{\cdot}048\text{M}|Ag} \underset{E_4}{\begin{matrix}\text{LiCl, 0·20M}\end{matrix}}$$

was measured, where MCl was HCl or LiCl. The E.M.F. was independent (to within ±1 mv) of the nature of MCl, and varied by only 10 mv when the concentration of MCl was varied from 0·064M to 0·64M. Since the total E.M.F. was the sum of E_1, E_2, E_3, and E_4 of which E_1 and E_4 were independent of the concentration and nature of MCl, it followed that the two liquid-junction potentials E_2 and E_3 were similarly affected by changes in the bridge solution, and there was no advantage in adding lithium chloride to the reference electrode (the mobilities in pyridine of the lithium and chloride ions are not known, and lithium chloride might not be the most suitable salt to use, but solubility considerations limit the choice). The E.M.F. of the above cell was some 150 mv, suggesting that silver ions and chloride ions in pyridine interact so as to reduce the silver-ion activity very considerably. Potentials measured relative to $Ag|AgNO_3$ and Ag|AgCl will thus not be comparable even when $[AgNO_3] = [AgCl]$.

FIG. 1. *Reference electrode.*



Measurement of the $Cu–Cu^+$ *Standard Potential,* E° (Cu, Cu^+).—In the system $Cu–Cu^+–Cu^{++}$ the reaction $Cu + Cu^{++} \rightleftharpoons 2Cu^+$ is possible, and therefore in general the potential of a copper electrode in a solution containing cuprous and cupric ions will not be stable relatively to a reference electrode if the system is not in equilibrium with respect to the above reaction, unless the velocity of approach to equilibrium is very low, so that a metastable state can persist. It was found that in pyridine the position of the above equilibrium lay so far over on the side of cuprous ion that even the purest cuprous chloride prepared (>99·5%) contained much more cupric ion than the equilibrium amount. Further, the velocity of the reaction $Cu + Cu^{++} \longrightarrow 2Cu^+$ was significant even at low cupric-ion concentration, so that a copper electrode immersed in a cuprous chloride solution containing 0·5% of cupric chloride rapidly became coated with a black film of cuprous salt, and stable potentials were not obtained. Still more rapid changes were observed when copper was brought into contact with a solution of cupric chloride in pyridine. The copper blackened, and the blue cupric solution became green and finally brown if reduction proceeded sufficiently far. The same colour changes were noted by Partington and Skeen (*loc. cit.*), who did not, however, interpret them and attempted unsuccessfully to use the electrode as a reference one. In order to obtain steady potentials it was therefore necessary to allow the reduction of the excess of cupric ion present in the cuprous chloride used to approach as closely to equilibrium as possible, and this entailed the provision of a large surface of copper and the extremely rigid exclusion of oxygen, since the oxidation of cuprous to cupric proceeds very rapidly, so much so that it provides a very efficient means of removing traces of oxygen.

Nitrogen, purified as described above, was bubbled through a reduction cell containing a cuprous chloride solution of known concentration and a large excess of copper powder, through the potentiometric cell proper, and finally through a copper–cuprous chloride–pyridine bubbler required to prevent back-diffusion of oxygen. The progress of the reduction was followed by measuring the potential of a platinum electrode in the reduction vessel relatively to a silver–silver nitrate reference electrode; this potential difference is approximately given by the equation

$$E = E^\circ\,(Cu^+, Cu^{++}) + (RT/F)\ln[Cu^{++}]/[Cu^+]$$

[where E° (Cu^+, Cu^{++}) is the cuprous–cupric standard potential] and therefore becomes less positive as $[Cu^{++}]/[Cu^+]$ decreases. After several hours, when reduction had gone as far as

possible, the cuprous chloride solution containing copper powder in suspension was blown over into the cell proper, and the potentials of the platinum and copper electrodes relatively to a silver–silver nitrate reference electrode were measured. These should of course be the same at equilibrium, but in fact equality was never achieved. This discrepancy, however, was not considered serious because it is clear that very small absolute changes in the cupric-ion concentration will have a large effect on the platinum electrode at the minute $[Cu^{++}]/[Cu^{+}]$ fraction established near equilibrium, whereas the copper electrode will be virtually independent of such changes provided that they do not alter the concentration of cuprous ion appreciably, and provided also that the rate of reduction of cupric ion at the copper electrode surface is negligible. The known low initial concentration of cupric ion ensured that the first condition was fulfilled, and the usual stability and reproducibility of the measured E.M.F. showed that the second one was also normally obeyed. The only exception was at the lowest cuprous chloride concentration used; the system was then most sensitive to traces of oxygen and it was correspondingly difficult to approach equilibrium closely. Under these conditions the copper electrode potential became steadily less negative with respect to the reference electrode, and the initial, most negative, value was taken. It was never possible tc reduce the cuprous chloride solution in the potentiometric cell proper, because the copper electrodes then became coated with a tenacious layer of cuprous chloride.

The results obtained are shown in Table 1, which includes two experiments in which lithium chloride was added to obtain a higher ionic strength than was possible with cuprous chloride alone.

TABLE 1.

Temp.	E (Pt),* mv	E (Cu), mv	[CuCl], M	E_0 (Cu, Cu^+), mv	Temp.	E (Pt),* mv	E (Cu), mv	[CuCl], M	E_0 (Cu, Cu^+), mv
18°	−540	−664	0·0064	−536	95°	−572	−641	0·0051	−475
18	−627	−675	0·0105	−559	95	−583	−617	0·0143	−483
18	−645	−670	0·0117	−558	95	−432	−584	0·0396	−481
18	−563	−630	0·050	−555	95	−503	−571	0·079	−490
18	−670	−685	0·0112 + [LiCl] = 0·189	−571	95	−651	−661	0·0112 + [LiCl] = 0·189	−518

* Lowest Pt potential.

The quantity E_0 (Cu, Cu^+) calculated from the equation

$$E = E_0 \text{ (Cu, } Cu^+) + (\boldsymbol{RT}/\boldsymbol{F})\ln[CuCl]$$

shows a definite drift with [CuCl], so that one or more of the assumptions implicit in the use of the equation are not strictly fulfilled in this case. The two most likely causes of error are incomplete dissociation of the cuprous chloride and variations in the activity coefficient of the cuprous ion, and the fact that a plot of E_0 (Cu, Cu^+) against (ionic strength)$^{\frac{1}{2}}$ (see, *e.g.*, Glasstone, " Textbook of Physical Chemistry," MacMillan, 1947, p. 942) gives a reasonably straight line suggests that the second is the main factor here. By extrapolating in this way to [CuCl] = 0, we have :

$$E_0 \text{ (Cu, } Cu^+) = -538 \text{ mv at } 18° = -477 \text{ mv at } 95°$$

relatively to the arbitrary silver–silver nitrate electrode described above.

Measurement of the Cu^+–Cu^{++} *Standard Potential* E_0 (Cu^+, Cu^{++}).—This quantity was determined by measuring the potential relatively to the reference electrode of a platinum electrode in pyridine containing various amounts of cupric and cuprous chlorides. These mixtures were prepared either by direct mixing of cupric and cuprous chloride solutions, or by titration of cuprous chloride solution with ferric chloride solutions in pyridine, the former being the more

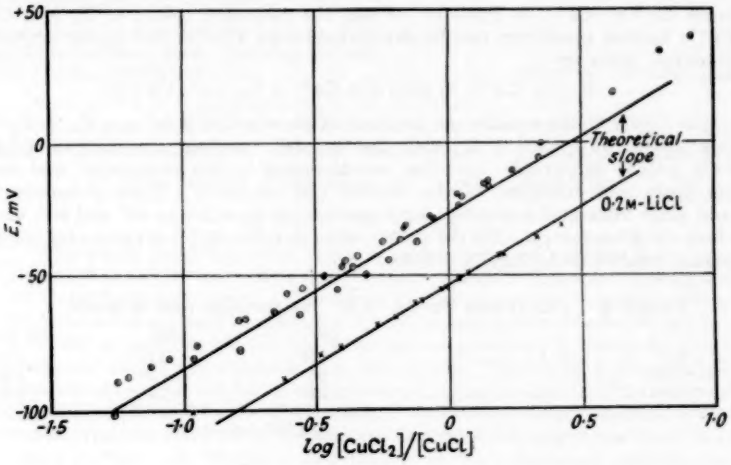
TABLE 2.

Temp.	[CuCl], M	[LiCl], M	E_0 (Cu^+, Cu^{++}), mv	Temp.	[CuCl], M	[LiCl], M	E_0 (Cu^+, Cu^{++}), mv
18°	*ca.* 0·002	—	−25	95°	*ca.* 0·002	—	+26
18	,,	0·2	−53	95	,,	0·2	−20

satisfactory method. The procedure adopted was to weigh the appropriate quantity of cuprous chloride directly into a known volume of pyridine in the potentiometric cell, through which a stream of nitrogen was passing, so that the cuprous chloride solution was protected from contact with air. Then either a cupric chloride solution or a ferric chloride solution of known concentration was added in successive portions from a burette. After each addition the E.M.F. of the cell became steady within a few minutes, and remained constant indefinitely.

The results are given in Table 2, the figures quoted each being the average of a number of experiments. Some measurements were again made in the presence of added lithium chloride, and show an effect due either to variations in activity coefficients or to specific interactions

FIG. 2.



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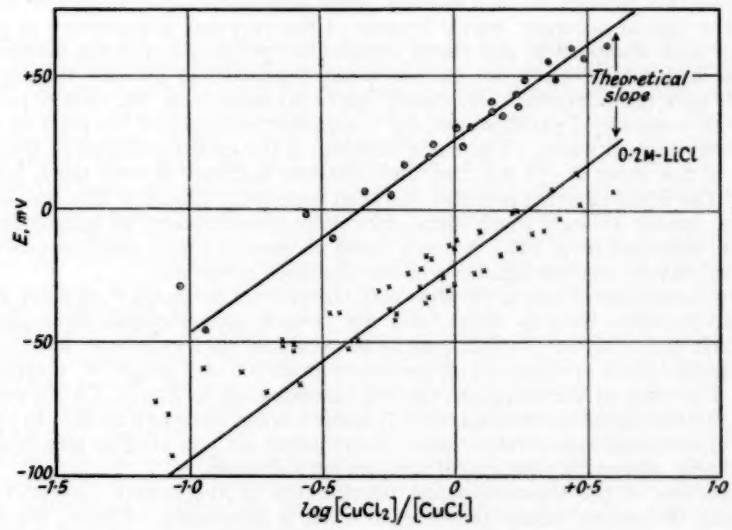

between chloride and cuprous and cupric ions. The quantity E_0 (Cu^+, Cu^{++}) has been calculated from the equation

$$E = E_0\ (Cu^+,\ Cu^{++}) + (\boldsymbol{RT}/\boldsymbol{F})\ln[CuCl_2]/[CuCl]$$

Figs. 2 and 3 show the graphs of log $[CuCl_2]/[CuCl]$ against E obtained at 18° and 95°, respectively. Reasonably straight lines were obtained, of slopes close to the theoretical values, particularly in absence of lithium chloride, suggesting that the assumptions implicit in the calculation of E_0 (Cu^+, Cu^{++}) are approximately correct at low ionic strengths. We have then

$$E_0\ (Cu^+,\ Cu^{++}) = -25 \text{ mv at } 18° = +26 \text{ mv at } 95°$$

relatively to the silver–silver nitrate reference electrode. According to Partington and Skeen (*loc. cit.*), E_0 (Cu^+, Cu^{++}) is 86 mv relatively to Ag|AgCl, 0·0265M, which gives 71 mv relatively to Ag|AgCl, 0·048M, it being assumed that the equation $E = E_0 + (\boldsymbol{RT/F}) \ln [AgCl]$ is obeyed. As pointed out, however, potentials determined relatively to $Ag|AgNO_3$ and Ag|AgCl, respectively, will not be directly comparable.

The System Cu–Cu^+–Cu^{++} *in Pyridine.*—From the measured values of E_0 (Cu, Cu^+) and E_0 (Cu^+, Cu^{++}) further quantities can be calculated; *e.g.*, E_0 (Cu, Cu^{++}), the copper–cupric standard potential, given by

$$E_0 (Cu, Cu^{++}) = \tfrac{1}{2}[E_0 (Cu, Cu^+) + E_0 (Cu^+, Cu^{++})]$$

and K, *i.e.*, $[Cu^{++}]/[Cu^+]^2$, the equilibrium constant of the reaction $2Cu^+ \rightleftharpoons Cu + Cu^{++}$, given by $(\boldsymbol{RT/F}) \ln K = E_0$ (Cu, Cu^+) $- E_0$ (Cu^+, Cu^{++}). ΔH, the heat absorbed in the reaction $2Cu^+ \longrightarrow Cu + Cu^{++}$ in pyridine, can also be calculated in the usual way, and hence the approximate heats and entropies of the various cell reactions. Table 3 summarizes the measured and some calculated quantities for the system in pyridine at 18° and 95°, and values calculated from the literature data for the same system in water at 25° are given for comparison; all potentials are relative to $Ag|AgNO_3$, 0·048M.

TABLE 3. *The system* Cu–Cu^+–Cu^{++} *in pyridine and in water.*

	18°	95°	25° (water)
E_0 (Cu, Cu^+), mv	−538	−477	−192
E_0 (Cu^+, Cu^{++}), mv	−25	+ 26	−560
E_0 (Cu, Cu^{++}), mv	−281	−225	−376
K, l. mole^{-1}	$1·4 \times 10^{-9}$	$1·3 \times 10^{-7}$	$1·5 \times 10^{6}$
ΔH	12,600 cals./mole		—

DISCUSSION

It appears that pyridine is not a medium which lends itself to potentiometric measurements of the highest accuracy, partly because of the very low conductivity of pyridine solutions of ionic compounds, and partly because the potentials of redox systems, even simple ones such as Cu^+–Cu^{++}, are far less firmly " poised " in pyridine than in water. Presumably both these drawbacks are mainly due to the same cause, *viz.*, the comparatively low dielectric constant of pyridine, and the consequent existence of ion pairs to a much greater extent than in water. The reproducibility of the results obtained in the present work was of the order of ± 5 mv, but their absolute accuracy is very much harder to estimate. The liquid-junction potential has been neglected; though it may well be large, it does not appear to vary much with electrolyte concentration, as judged from the experiments described on p. 3475, and will therefore scarcely affect quantities such as K which are calculated from the difference of two measured potentials.

Activity coefficients of ions in pyridine may be expected to depart from unity at much lower ionic strengths than in water, and the present measurements show anomalies [*e.g.*, the drift in E_0 (Cu, Cu^+)] which seem to be caused by such variations, but there may also be a specific effect of chloride ions due to the formation of $(CuCl_n)^{(n-1)-}$ complexes, as in water. The effect of increasing chloride-ion concentration on E_0 (Cu, Cu^+) is not, however, large, so that complex formation can only occur to a small extent if at all. In contrast, increasing chloride-ion concentration causes the apparent activity of silver ions in pyridine to fall markedly, presumably because of complex-ion formation.

A comparison of the thermodynamic relationships of the system Cu–Cu^+–Cu^{++} in pyridine with the corresponding quantities in water is interesting. Clearly, the relative stability of cuprous and cupric ions in the presence of copper metal is completely reversed by the change of solvent, and this change must be due to the difference in the relative free energies of solvation of the two ions. Numerous pyridine–copper complexes are of course known, including pyridine–cupric ones, but from the above figures the latter must be less stable than the pyridine–cuprous complexes. This strong solvation of the cuprous ion is presumably responsible for the relatively small formation of cuprous ion–chloride ion complexes in pyridine. Since silver ion–chloride ion complex formation is apparently more marked, silver ions in pyridine must be less strongly solvated.

The experiments with a hydrogen electrode in pyridine indicate the possibility of

expressing potentials in pyridine on the hydrogen scale, as is conventional for aqueous systems, but for most purposes no advantage would be gained by doing so. A more important application of the hydrogen electrode in pyridine would be for the measurement of pyridinium-ion concentrations, making possible acid–base titrations and dissociation-constant measurements as in water.

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667. *Electrochemical Measurements in Pyridine. Part II.* The Redox Potentials of Some Quinones.*

By A. K. GUPTA.

The redox potentials of a series of quinone–quinol systems have been measured in anhydrous pyridine, and in some cases the entropies of reduction have also been determined. The use of this solvent allows measurements to be made on compounds where this had been impracticable because of their low solubility in water or alcohol, including higher polycyclic quinones for which predicted values are available for comparison. Sufficient agreement has been found between calculated and measured values to show that the empirical relations used to predict redox potentials are of considerable practical value, but appreciable discrepancies exist, and the possible reasons for these have been discussed. In the case of anthraquinone, the reduction to anthraquinol anion in anhydrous pyridine has also been investigated, and a very large semiquinone formation constant found.

A KNOWLEDGE of the free energies of reduction of the carbonyl groups of quinones is of practical importance in connection with vat dyes, and of theoretical interest because such free energies can, with certain limitations, be correlated with structure in a large number of cases (Branch and Calvin, "Theory of Organic Chemistry," Prentice-Hall, **1945**; Diatkina and Syrkin, *Acta Physicochim. U.R.S.S.*, 1946, **21**, 921; Carter, *Trans. Faraday Soc.*, 1949, **45**, 597; Evans, *ibid.*, 1946, **42**, 113), and also in many cases with the rates of reduction of quinones or with the rates of oxidation of quinols (Barron, *J. Biol. Chem.*, 1932, **97**, 287; Dimroth, *Z. angew. Chem.*, 1933, **46**, 571; Hammett and Pfluger, *J. Amer. Chem. Soc.*, 1933, **55**, 1079). The measurement of redox potentials affords an extremely convenient method for determining free energies of reduction, but in the usual solvent, water, its application is limited by solubility difficulties. Its range can be somewhat extended by the use of alcohol as solvent (Kvalnes, *ibid.*, 1934, **56**, 670; Fieser and Fieser, *ibid.*, p. 1565) or by using mixtures of water and organic solvents (Geake and Lemon, *Trans. Faraday Soc.*, 1938, **34**, 1409), but the redox potentials of most vat dyes remain inaccessible, as do those of the unsubstituted polycyclic quinones which are of particular interest in testing proposed relationships between structure and redox potential. Sulphuric acid is a good solvent for these compounds, but attempted measurements in that medium have had only limited success (Geake, *ibid.*, 1941, **37**, 68).

In the present work the technique developed in Part I * for potentiometric measurements in anhydrous pyridine has been used to determine the redox potentials in that solvent of a number of quinones and other compounds, in some cases at two different temperatures, the process studied being the reduction to the leuco-compounds by addition of hydrogen atoms. The reduction of quinones to their leuco-anions by addition of electrons is of greater interest from the technical point of view, and the redox potential of the system anthraquinone–anthraquinol anion was measured in pyridine, but the experimental difficulties proved so great that no other compounds were investigated under the same conditions. Potentiometric measurements proved generally more difficult in pyridine than in water, and could not be made with the same accuracy, but the potentials

* Part I, preceding paper.

observed in pyridine were sufficiently stable and reproducible in most cases to yield useful information. As in water, the main limitation was still set by solubility considerations; some of the compounds (especially pyranthrone) were only very slightly soluble even in pyridine, and their solutions consequently gave less well poised potentials. This tendency was more marked at higher temperatures, presumably because of insulation difficulties, and in the worst cases the potentials were then too unsteady to measure. In addition, measurements above room temperature could not be made on *p*-benzoquinone or 1 : 4-dibenzamidoanthraquinone, in the first case because of reaction with pyridine hydrochloride (presumably to give a halogenated quinol), and in the second because of decomposition of the reduced compound.

Systems Q–QH_2.—The significance of the potential–composition curves obtained was tested by applying the usual equation

$$E = E_0 + (\boldsymbol{RT}/\boldsymbol{F}) \ln [H^+] + (\boldsymbol{RT}/2\boldsymbol{F}) \ln [\text{ox.}]/[\text{red.}] \quad . \quad . \quad . \quad . \quad (1)$$

where $[H^+]$ = concentration of pyridine hydrochloride, *i.e.*, complete ionization of the latter is assumed and the pyridinium ion is taken as equivalent to the H_3O^+ ion in water; [ox.] = concentration of total oxidised form; [red.] = concentration of total reduced form; and $[H^+] \gg$ [ox.] + [red.]. The assumptions implicit in equation (1) appeared to be reasonably justified at constant ionic strength, since the calculated E_0 values were constant in each case to ± 3 mv or better over the range 20—80% oxidised, the reproducibility in successive experiments being of the same order, except for pyranthrone. If, however, the ionic strength was varied, by varying the pyridine hydrochloride concentration or by adding a neutral salt, E_0 varied appreciably, as shown in Table 1.

TABLE 1. (Quinone concentration 0·001M throughout.)

Temp.	[HCl], M	[LiCl], M	E_0 (anthraquinone), mv	Temp.	[HCl], M	[LiCl], M	E_0 (anthraquinone), mv
18°	0·013	—	−298	18°	0·049	0·124	−346
,,	0·049	—	−308	95	0·090	—	−406
,,	0·115	—	−329	,,	0·194	—	−420
,,	0·216	—	−332	,,	0·232	—	−421
,,	0·61	—	−349				

It seems likely that the variations represent changes in activity coefficients, but no attempt was made to correct for these. Instead, measurements were made throughout at an ionic strength of approximately 0·2. The results are shown in Table 2.

TABLE 2.

Compound	E_0 (T_1°), mv		E_0 (T_2°), mv		ΔS, cal. °C^{-1} mole^{-1}
p-Benzoquinone	199	(25°)	—		—
1 : 4-Naphthaquinone	− 23	(18°)	—		—
9 : 10-Anthraquinone	−332	(18°)	−420	(95°)	51
9 : 10-Phenanthraquinone	− 21	(25°)	− 60	(95°)	25
Perylene-3 : 10-quinone	0	(25°)	− 51	(95°)	41
Anthanthrone	−238	(25°)	—		—
3 : 4-8 : 9-Dibenzopyrenequinone	−242	(25°)	−287	(75°)	41·5
Pyranthrone	*ca.* −330	(25°)	—		—
Dibenzanthrone	−222	(18°)	—		—
1 : 4-Dibenzamidoanthraquinone	−410	(18°)	—		—
16 : 17-Dimethoxydibenzanthrone	−277	(18°)	−305	(70°)	25
Indanthrone	−223	(25°)	—		—
Indigo	−220	(25°)	—		—

Branch and Calvin (*op. cit.*) and Carter (*loc. cit.*) have given empirical relationships between the relative redox potentials of a series of unsubstituted quinones and the numbers of Kekulé forms of the quinones and the corresponding quinols, and have tested these relations for compounds with up to 5 rings by comparison with values determined in alcoholic solution. The present work allows a test to be made for compounds with up to 9 rings.

Table 3 gives the experimental values at room temperature and those calculated from Carter's equation, their zero being adjusted to make $\Sigma[E_0 \text{ (exp.)} - E_0 \text{ (calc.)}]^2$ a minimum.

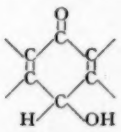
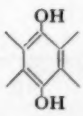
The agreement between the experimental and the calculated redox potentials is certainly sufficient to give information of practical value with a quinone of unknown potential, but the larger deviations are clearly outside the range of experimental error. It is therefore of interest to examine possible reasons for the discrepancies.

Both Carter's and Branch and Calvin's methods for calculating redox potentials depend on the assumptions that reduction takes place exclusively to the quinol; that the relative free energies of reduction of a series of quinones depend almost exclusively on the differences in resonance energy between quinones and quinols; that the resonance energies can be represented by an equation which takes account of Kekulé forms only; and finally, that steric " ortho "-effects can be allowed for by a small number of empirical corrections.

TABLE 3.

	E_0 (exp.), mv	E_0 (calc.), mv	Diff., mv		E_0 (exp.), mv	E_0 (calc.), mv	Diff., mv
p-Benzoquinone	199	205	− 6	Anthanthrone	−238	−291	+53
1 : 4-Naphthaquinone	− 23	− 30	+ 7	3 : 4-8 : 9-Dibenzo-pyrenequinone	−242	−274	+32
9 : 10-Anthraquinone...	−332	−342	+10	Pyranthrone ..... *ca.*	−330	−316	−14
9 : 10-Phenanthra-quinone	− 21	+ 2	−23	Dibenzanthrone	−222	−258	+36
3 : 10-Perylenequinone	0	+ 87	−87				

The validity of the first assumption is seldom questioned, yet the possibility always exists of reduction to the keto-form (I) tautomeric with the quinol (II). In the case of anthraquinone the keto-form (oxanthrone) is well known, though the normal equilibrium between (I) and (II) lies at 97% of (II) in alcohol (Meyer, *Annalen*, 1911, **379**, 37). Data on keto–enol equilibria for other quinols are scanty, but the considerations used to predict

(I)   (II)

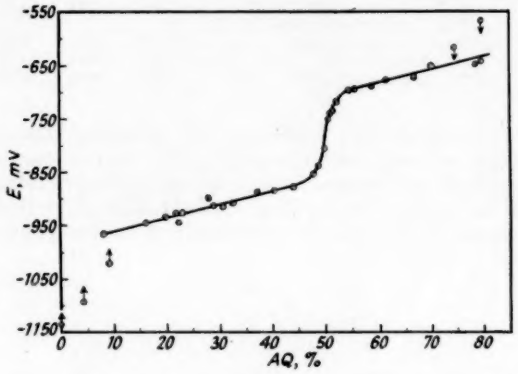
the relative free energies of the change quinone→ quinol for a series of compounds should be equally applicable to predicting the relative free energies of the change (I)→(II). Hence, structures which favour the quinone relatively to the quinol should also favour the oxanthrone form, and, solvent effects apart, the greatest equilibrium proportion of keto-form would be expected in the reduction products of those quinones with the lowest predicted redox potentials; but, in fact, [E_0 (exp.) − E_0 (calc.)] does not seem to vary systematically with E_0 (calc.), and it appears either that no appreciable amount of keto-form is produced from any of the quinols, or that the same proportion is formed in all cases. The former is the more likely explanation, since in alcohol only 3% of keto-form occurs at equilibrium with anthraquinol, even though anthraquinone has one of the lowest predicted redox potentials.

The second assumption has been discussed by Evans and de Heer (*Quart. Reviews*, 1950, **4**, 94), who point out that the differences in the heats and entropies of solvation of quinones and quinols are the most likely factors to vary, apart from the differences in resonance energies, and that the entropy of reduction, for example, varies with the solvent. Table 2 shows that for four unsubstituted quinones in pyridine the entropy of reduction varies considerably, but it is surprising that in spite of the large entropy contribution to the total free-energy change, these variations in ΔS are not reflected in E_0(exp.) − E_0(calc.). The conclusion seems to be that the heat change of reduction is also varying appreciably, in such a way as to obscure the effect of the variations in ΔS. Direct measurement of heats of solvation would throw light on this point.

The third assumption has been tested by Carter (*loc. cit.*), who has shown that his empirical equation agrees surprisingly well with the results of molecular-orbital calculations, even up to undecacyclic compounds. The fourth assumption may well be partly incorrect, and individual corrections may be needed if a wide range even of unsubstituted compounds is to be covered, but as Evans and de Heer have pointed out, the nature of these " ortho "-

effects is not always clear, and quantitative treatment of them is usually impossible. In any case the observed variation of ΔS, and the probable accompanying variation of ΔH, are amply large enough to account for the observed discrepancies without involving further variables.

System Q–Q$^-$.—The potential–composition curve obtained for the system anthraquinone–anthraquinol anion in pyridine at 18° is shown in the figure. Analysis by Michaelis and Schubert's method (*Chem. Reviews*, 1938, **22**, 437) showed that the potentials measured were in fact thermodynamically significant, and that the reaction $AQ^- \rightleftharpoons AQ + 2e$ proceeds in two distinct one-electron steps, the free energies of which are so different that the first is completed before the second occurs to any appreciable extent. Consequently, an equimolecular mixture of AQ and AQ$^-$ in pyridine consists almost entirely of the semiquinone SQ$^-$ formed by the reaction $AQ + AQ^- \rightleftharpoons 2SQ^-$, for which the equilibrium constant $K = [SQ^-]^2/[AQ][AQ^-]$ is in this case *ca.* 5×10^4. No



Redox curve of AQ–AQ$^-$ *in pyridine at* 18° C.

dimerization of the semiquinone could be detected. From the results its appears that E_1 and E_2, the standard potentials of the steps

$$AQ + e \longrightarrow SQ^- \ (E_1) \qquad SQ^- + e \longrightarrow AQ^- \ (E_2)$$

are respectively −635 and −922 mv.

Geake and Lemon (*loc. cit.*) observed a large increase in K for anthraquinone from water to 50% mixtures of water with pyridine, morpholine, Cellosolve, or ethylenediamine, and it now appears that K continues to increase in going to 100% pyridine. Since this effect of organic solvents in increasing K does not seem to require the presence in the solvent of any particular atom or group, the most likely explanation of their action is that they affect the dielectric constant of the medium. The lower the dielectric constant, the greater will be the electrostatic repulsion barrier to the process $2SQ^- \longrightarrow AQ + AQ^-$, while the reverse process will be relatively unaffected. As the dielectric constant falls, both SQ$^-$ and AQ$^-$ will tend to form ion-pairs with the cations present, and the two tendencies will very roughly counterbalance each other. In general, therefore, semiquinone formation should be favoured by a lowering of the dielectric constant of the medium, at the expense of both AQ and AQ$^-$, and of any semiquinone dimer.

It is interesting that the semiquinone derived from anthraquinone is only feebly coloured, its solutions in pyridine being pale brown (cf. Geake and Lemon, *loc. cit.*). Presumably it has a strong absorption band outside the visible spectrum.

Finally, by combining the results of the measurements on the AQ–AQH$_2$ and AQ–AQ$^-$ systems, a value can be derived for the dissociation constant $K_A = [AQ^-][H^+]^2/[AQH_2]$, which is found to be 4×10^{-16} g.-mol.^{2}/l.^{2} in pyridine. A roughly comparable value is that for anthraquinol-β-sulphonate in water, found by Conant *et al.* (*J. Amer. Chem. Soc.*, 1922, **44**, 1882) to be 5×10^{-20}. The dissociating effect of the more basic solvent is clear.

Experimental

Unless otherwise stated, anhydrous materials of analytical reagent quality were used as such. Pyridine was purified as described in Part I (*loc. cit.*), and pyridine hydrochloride solutions were made by absorbing dry hydrogen chloride in anhydrous pyridine, the concentration being estimated by diluting aliquot portions ten-fold with water and titrating with phenolphthalein as indicator. The majority of the quinones investigated were prepared and purified by the late Dr. P. G. Carter. 3 : 10-Perylenequinone was made from perylene prepared by Dr. Carter, by oxidation with chromic acid followed by recrystallization from nitrobenzene and pyridine. Anhydrous ferric chloride (B.D.H.) and a commercial sample of sodium methoxide were stored *in vacuo* and used as such.

The purification of nitrogen and hydrogen, and the apparatus used, were as described in Part I. The procedure for measurements on the Q–QH_2 systems was to prepare a solution of the reduced form of a given compound in pyridine containing 0·2M-pyridine hydrochloride, and to titrate this solution potentiometrically with an oxidizing agent such as ferric chloride, also dissolved in pyridine. Alternatively, varying amounts of the oxidized form were added to a known amount of the reduced form. Since most of the reduced forms could not be prepared in air, solutions of the oxidized forms were reduced in the potentiometric cell itself, by using hydrogen and the minimum quantity of palladized or platinized asbestos, prepared by alkaline formaldehyde reduction of palladium or platinum chloride absorbed on asbestos-flock. Before the titration was started, residual hydrogen was displaced by nitrogen. It was shown that pyridine was not hydrogenated under the conditions used to reduce the quinones.

For measurements on AQ–AQ^-, solutions of anthraquinone were reduced in pyridine and treated under nitrogen with an excess of sodium methoxide, and the resulting solutions of the sodium salt of anthraquinol were filtered into a burette fitted to the potentiometric cell. Titrations were carried out either by adding a standard anthraquinone solution to a known amount of the standard solution, or *vice versa*. Titration of the anthraquinol anion with a wide variety of inorganic and organic oxidizing agents was attempted, but without success, apparently because of the electrochemical sluggishness of the anthraquinone–anthraquinol anion system, together with its reluctance to enter into chemical equilibrium with other redox systems. Even in the absence of interfering systems, stable potentials were only very slowly established, particularly near the 50% point, where several hours were required for the attainment of equilibrium after each alteration of composition, and below 20% and above 80% of oxidized form. This sluggishness, together with the extreme sensitivity to oxidation of AQ^- and the low working concentration required by its comparatively low solubility, made necessary the most rigorous exclusion of oxygen from the apparatus.

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668. *Reactions of Fluorocarbon Radicals. Part VI.* The Hydration of Trifluoromethyl- and Pentafluoroethyl-substituted Acetylenes.*

By R. N. Haszeldine and K. Leedham.

The synthesis of 3 : 3 : 4 : 4 : 4-pentafluorobut-1-yne (pentafluoroethylacetylene) by reaction of pentafluoroiodoethane with acetylene, followed by dehydroiodination, is reported. Mercury-catalysed hydration of 3 : 3 : 3-trifluoropropyne at room temperature yields 1 : 1 : 1-trifluoroacetone and 3 : 3 : 3-trifluoropropaldehyde in the ratio of 2 : 1; at higher temperatures the ketone and βββ-trifluoropropionic acid are formed. The pentafluorobutyne similarly yields 3 : 3 : 4 : 4 : 4-pentafluorobutan-2-one and ββγγγ-pentafluorobutyric acid. A mechanism for the hydration of acetylenes is proposed and discussed, and infra-red and ultra-violet spectra of certain fluorine compounds are presented.

Syntheses for 3 : 3 : 3-trifluoropropyne were described in Parts IV and V (Haszeldine, *J.*, 1951, 588, 2495). The present communication (see Abstracts 120th Meeting Amer. Chem. Soc., New York, Sept. 1951, 7K) is concerned with the synthesis of 3 : 3 : 4 : 4 : 4-pentafluorobut-1-yne and with the hydration of this and of 3 : 3 : 3-trifluoropropyne.

* Part V, Haszeldine, *J.*, 1951, 2495.

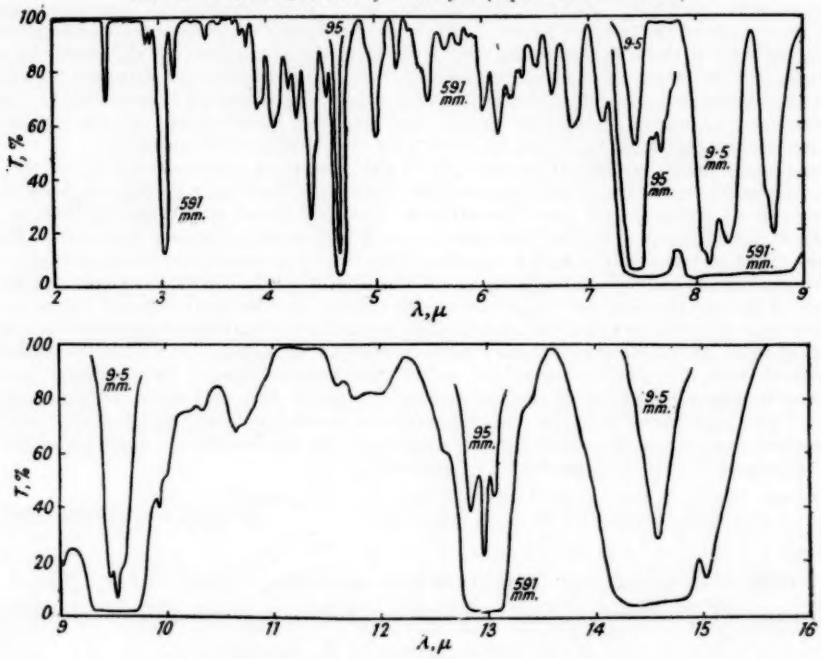
Pentafluoroiodoethane and acetylene do not react in the dark at room temperature, but on exposure to ultra-violet light a smooth reaction occurs to yield compounds of the general formula $C_2F_5{\cdot}[CH{:}CH]_n{\cdot}I$:

$$C_2F_5{\cdot} + CH{:}CH \longrightarrow C_2F_5{\cdot}CH{:}CH{\cdot} \xrightarrow{C_2F_5I} C_2F_5{\cdot}CH{:}CHI + C_2F_5{\cdot}, \text{ etc.}$$

The compound where $n = 1$, *viz.*, 3 : 3 : 4 : 4 : 4-pentafluoro-1-iodobut-1-ene, is the main product, but small amounts of the compound where $n = 2$, *viz.*, 5 : 5 : 6 : 6 : 6-pentafluoro-1-iodohexa-1 : 3-diene, have been isolated and characterised. The interaction of pentafluoroiodoethane and acetylene takes place in absence of light at 210—240° and yields similar products.

Dehydroiodination of 3 : 3 : 4 : 4 : 4-pentafluoro-1-iodobut-1-ene with powdered potassium hydroxide gives pentafluorobut-1-yne, from which copper, silver, and mercuric

FIG. 1. 3 : 3 : 3 : 4 : 4-*Pentafluorobutyne* (*vapour in* 50 *mm. cell*).



acetylides are prepared in the standard manner. The infra-red spectrum of pentafluorobutyne is shown in Fig. 1. The acetylenic carbon–hydrogen and the C≡C stretching frequencies are at 3·01 and 4·66 μ (cf. trifluoropropyne 3·01, 4·65 μ; propyne 2·96, 4·625 μ).

Details for the preparation of 3 : 3 : 3-trifluoropropyne from trifluoroiodomethane in 56% yield by the sequence

$$CF_3I \xrightarrow{C_2H_4} CF_3{\cdot}CH_2{\cdot}CH_2I \xrightarrow{-HI} CF_3{\cdot}CH{:}CH_2 \xrightarrow{Br_2} CF_3{\cdot}CHBr{\cdot}CH_2Br$$

$$\downarrow -HBr$$

$$CF_3{\cdot}C{:}CH \xleftarrow{Zn,\ EtOH} CF_3{\cdot}CBr{:}CHBr \xleftarrow{-HBr} CF_3{\cdot}CBr_2{\cdot}CH_2Br \xleftarrow{Br_2} CF_3{\cdot}CBr{:}CH_2$$

are given in the Experimental section. This route is applicable to the higher fluoro-iodides and on an autoclave scale provides the most convenient method for the preparation of larger quantities of the (perfluoroalkyl)acetylenes.

The ionic addition of HX (X = F, Cl, Br, I, OMe, OEt, NR_2) to trifluoropropyne has been found to yield $CF_3{\cdot}CH{:}CHX$ (see following paper), *i.e.*, a reversal of the direction of addition compared with propyne, and indicating a polarisation $F_3C{\leftarrow}\overset{\delta-}{C}{\equiv}\overset{\delta+}{C}H$. Thus, trifluoropropyne might be expected to yield an aldehyde on hydration :

$$CF_3{\cdot}C{:}CH \xrightarrow{H_2O} CF_3{\cdot}CH{:}CH{\cdot}OH \longrightarrow CF_3{\cdot}CH_2{\cdot}CHO$$

rather than the ketone usually obtained by hydration of 1-alkynes.

The trifluoropropyne and pentafluorobutyne are recovered unchanged from dilute sulphuric acid even after being heated to 120°, indicating that, as in trifluoropropene, the perfluoroalkyl group tends to deactivate the adjacent unsaturated linkage. The hydration of trifluoropropyne proceeds smoothly at room temperature, however, when mercuric sulphate is added to the sulphuric acid, and after several days a mixture of βββ-trifluoropropaldehyde and 1 : 1 : 1-trifluoroacetone is produced :

$$CF_3{\cdot}C{:}CH \longrightarrow CF_3{\cdot}CH_2{\cdot}CHO + CF_3{\cdot}CO{\cdot}CH_3$$

This can be separated by conversion of the aldehyde into the dimedone derivative and of the residual ketone into the 2 : 4-dinitrophenylhydrazone. The ratio of aldehyde : ketone is 1 : 2.

The mercury-catalysed hydration thus yields mainly the ketone and not the aldehyde expected from the polarisation. With other acetylenes the hydration product is that predicted on general grounds. Thus, αβ-acetylenic acids or nitriles give the corresponding β-keto-acids [$R{\cdot}\overset{\delta+}{C}{\equiv}\overset{\delta-}{C}{\cdot}CO_2H \longrightarrow R{\cdot}CO{\cdot}CH_2{\cdot}CO_2H$, where R = alkyl, Ph, *p*-$NO_2{\cdot}C_6H_4$, *p*-$Br{\cdot}C_6H_4$, *o*-$NH_2{\cdot}C_6H_4$, or Cl (Zernik, *Apoth. Ztg.*, 1904, **20**, 382; *Chem. Zent.*, 1905, I, 1728; Moureu and Delange, *Compt. rend.*, 1901, **132**, 1121; 1903, **136**, 552, 753; *Bull. Soc. chim.*, 1903, **29**, 648, 666, 676; Reimer and Tobin, *J. Amer. Chem. Soc.*, 1941, **63**, 2490)], and hydration of acetylenic ketones gives β-diketones [$R{\cdot}CO{\cdot}\overset{\delta-}{C}{\equiv}\overset{\delta+}{C}R' \longrightarrow R{\cdot}CO{\cdot}CH_2{\cdot}COR'$, where R and R′ = alkyl, aryl, etc. (Nef, *Annalen*, 1899, **308**, 277; Yvon, *Compt. rend.*, 1925, **180**, 748; Moureu and Delange, *Bull. Soc. chim.*, 1901, **25**, 306; *Ann. Chim.*, 1914, **2**, 277; Fuson, Ullyot, and Hickson, *J. Amer. Chem. Soc.*, 1939, **61**, 410; Morton, Hassan, and Calloway, *J.*, 1934, 883)]. Similarly, alkoxyacetylenes give the expected ester [*e.g.*, $Bu{\cdot}\overset{\delta-}{C}{\equiv}\overset{\delta+}{C}OPh \longrightarrow Bu{\cdot}CO_2Ph$ (Jacobs, Cramer, and Weiss, *J. Amer. Chem. Soc.*, 1940, **62**, 1849)]. With monosubstituted acetylenes, the hydration of 1-alkynes invariably yields the 2-ketone, and alkoxyacetylenes give the ester [$H\overset{\delta-}{C}{\equiv}\overset{\delta+}{C}{\cdot}OR \longrightarrow CH_3{\cdot}CO_2R$, R = Et, Bu (Jacobs, Cramer, and Hanson, *ibid.*, 1942, **64**, 223)] whether water, sulphuric acid, or sulphuric acid in the presence of mercuric sulphate be used as hydrating agent. It is thus significant that the monosubstituted acetylene, ethynyl phenyl ketone, is hydrated to 1-phenylpropane-1 : 2-dione in the presence of mercuric sulphate [$Ph{\cdot}CO{\cdot}C{:}CH \longrightarrow Ph{\cdot}CO{\cdot}CO{\cdot}CH_3$ (Bowden, Braude, and Jones, *J.*, 1946, 945)], despite the α-carbonyl group which would be expected to favour the formation of the 1 : 3-dione. The hydration of ethynyl phenyl ketone clearly resembles that of $R{\cdot}C{:}CH$ (R = CF_3, C_2F_5), and the following general scheme is advanced to explain the apparent anomaly.

It is suggested that two competing reactions are involved in the hydration of $R{\cdot}C{:}CH$ (R = CF_3, C_2F_5, COPh, etc.). (*a*) The aldehyde is formed *via* an intermediate complex formed by addition of HgY_2 (Y = HSO_4, say, in acid solution) followed by addition of water and loss of HgY_2 (cf. Hennion, Vogt, and Nieuwland, *J. Org. Chem.*, 1936, **1**, 159). The direction of addition of HgY_2 is determined by the group R :

$$R{\cdot}\overset{\delta-}{C}{\equiv}\overset{\delta+}{C}H \xrightarrow{HgY_2} R{\cdot}C(HgY){:}CHY \xrightarrow[-HgY_2]{+H_2O} R{\cdot}CH{:}CH{\cdot}OH \longrightarrow R{\cdot}CH_2{\cdot}CHO$$

(*b*) A compound of the type $R{\cdot}C{:}C{\cdot}HgY$, or the mercuric acetylide, is postulated as the initial reversible step, which is followed by the rapid addition of HgY_2. The direction of addition of HgY_2 is now reversed compared with (*a*), since the mercury attached

directly to the acetylenic carbon atom will exert a greater influence on the unsaturation electrons of the triple bond than will the fluorine atoms on a carbon atom once removed from the triple bond, and the ketone is produced regardless of the nature of R :

$$R\cdot C{:}CH \rightleftharpoons R\cdot \overset{\delta+}{C}\equiv \overset{\delta-}{C}\cdot HgY \xrightarrow{HgY_2} R\cdot CY{:}C(HgY)_2 \xrightarrow[HgY_2]{H_2O,HY} R\cdot C(OH){:}CH_2 \longrightarrow R\cdot CO\cdot CH_3$$

Schemes (*a*) and (*b*) would yield the same product, the ketone, when R = alkyl or an electron-supplying group.

A white solid complex is formed as soon as the (perfluoroalkyl)acetylenes and mercuric sulphate are mixed in presence of sulphuric acid, but attempts to purify and analyse the complex (which is not the known low-melting mercuric perfluoroalkylacetylide) have been unsuccessful. Since the acetylenic hydrogen atom is essential in scheme (*b*), the hydration of 1 : 1 : 1-trifluorobut-2-yne is being investigated, since this should yield 4 : 4 : 4-trifluorobutan-2-one ($CF_3\cdot C{:}C\cdot CH_3 \longrightarrow CF_3\cdot CH_2\cdot CO\cdot CH_3$).

The hydration of the (perfluoroalkyl)acetylenes has also been investigated at higher temperatures. When traces of mercuric sulphate were used at 130°, complete reduction to mercury took place, at which stage the hydration stopped. Trifluoroacetone and traces of βββ-trifluoropropionic acid were formed, but 3 : 3 : 3-trifluoropropaldehyde could not be detected. When an excess of mercuric sulphate was used as catalyst at 135°, the trifluoropropyne underwent rapid and complete reaction, and free mercury was not evident. The volatile reaction products were 1 : 1 : 1-trifluoroacetone, fluoroform, and carbon dioxide;

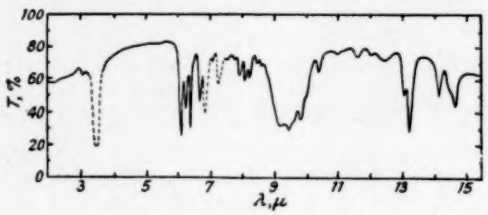


FIG. 2. *Nitron derivative of* $CF_3\cdot CH_2\cdot CO_2H$.

3 : 3 : 3-trifluoropropaldehyde was not detected, but the aqueous solution contained βββ-trifluoropropionic acid, characterised as its nitron salt and as the urea derivative (I; R = NMe_2, R′ = CF_3). The nitron salts are readily obtained from fluoro-acids of general formula $CF_3\cdot[CF_2]_n\cdot[CH_2]_m\cdot CO_2H$ (*m* = 0 or 1), which are appreciably stronger acids than

(I) *p*-$R\cdot C_6H_4\cdot NH\cdot CO\cdot N(CO\cdot CH_2R')\cdot C_6H_4R$-*p* $\qquad$ $C(:N\cdot C_6H_4R\text{-}p)_2$ (II)

their hydrocarbon analogues. Since the nitron salts decompose on heating, they are best characterised by their infra-red spectra (*e.g.*, see Fig. 2). Fluoro-acids of the above formula with $m \geqslant 1$ are more readily characterised by their ready reaction with carbodi-imines (II) (Schall, *J. pr. Chem.*, 1901, **64**, 261; Zetzsche, Lüscher, and Meyer, *Ber.*, 1938, **71**, 1088; Zetzsche and Röttger, *ibid.*, 1940, **73**, 50, introduced this reagent for the characterisation of carboxylic acids). Derivatives of sharp m. p. and characteristic infra-red spectra are obtained. Comparison of the urea derivative (I; R = NMe_2, R′ = CF_3) with a specimen obtained from βββ-trifluoropropionic acid prepared by the sequence (Haszeldine, *Nature*, 1951, **168**, 1028)

$$CF_3I \longrightarrow CF_3\cdot CH_2\cdot CH_2I \longrightarrow CF_3\cdot CH_2\cdot CH_2\cdot MgI \longrightarrow CF_3\cdot CH_2\cdot CH_2\cdot OH \longrightarrow CF_3\cdot CH_2\cdot CO_2H$$

confirmed the identity of the hydration product from trifluoropropyne.

Pentafluorobutyne similarly showed no reaction with dilute sulphuric acid at 110° but on addition of an excess of mercuric sulphate the alkyne was rapidly converted into 3 : 3 : 4 : 4 : 4-pentafluorobutan-2-one, carbon dioxide, and pentafluoroethane. The fluoroketone, which readily forms a hydrate, was characterised by its 2 : 4-dinitrophenylhydrazone. The presence of ββγγγ-pentafluorobutyric acid in the aqueous phase was shown by the formation of the urea derivative (I; R = NMe_2, R′ = C_2F_5). Salt formation between the

βββ-trifluoropropionic or ββγγγ-pentafluorobutyric acids and the dimethylamino-group, in preference to acyl-urea formation, can be excluded, since the infra-red spectra of derivatives (I) show the acyl carbonyl band at 5·81 μ, and the strong band at 4·77 μ present in the spectrum of the parent carbodi-imine (II; R = NMe_2) is no longer apparent.

The formation of trifluoropropionic and pentafluorobutyric acids is attributed to the thermal oxidation of the aldehydes whose presence can be demonstrated at lower temperatures and may be associated with the formation of mercury from mercuric sulphate. The carbon dioxide produced during reaction did not arise by decarboxylation of the fluoro-acids, since 1 : 1 : 1-trifluoroethane and 1 : 1 : 1 : 2 : 2-pentafluoropropane were not isolated.

The infra-red spectra of 1 : 1 : 1-trifluoroacetone and 3 : 3 : 4 : 4 : 4-pentafluorobutan-2-one are shown in Fig. 3. The carbonyl stretching vibrations are at the remarkably low wave-lengths of 5·63 and 5·65 μ (cf. 5·85 μ for an alkyl ketone), providing another example of the shift to lower wave-length of the " characteristic " wave-length of functional groups noted earlier (Haszeldine, *Nature*, 1951, **168**, 1028). The carbon–hydrogen stretching vibration appeared at 3·33 μ in both compounds, and the bands at 7·00 and 7·25 and at 7·03 and 7·30 μ, respectively, may be associated, at least in part, with the carbon–hydrogen bending vibrations of the methyl groups. The pattern of the strong bands in the

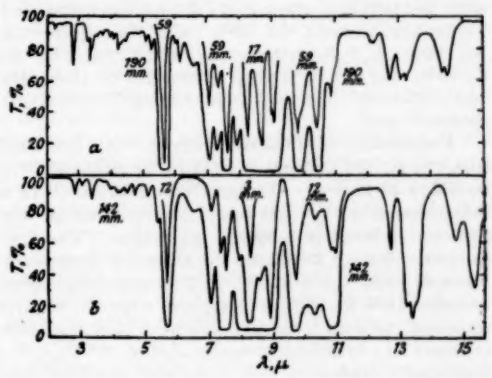


FIG. 3.

(*a*) CF_3·CO·CH_3. *Vapour in 50-mm. cell.*
(*b*) C_2F_5·CO·CH_3. *Vapour in 50-mm. cell.*

8—9 μ region of the spectrum due to the carbon–fluorine stretching vibrations easily distinguishes the homologous ketones.

EXPERIMENTAL

Preparation of Trifluoroiodomethane and Pentafluoroiodoethane.—Trifluoroiodomethane was prepared from silver trifluoroacetate and iodine (Haszeldine, *J.*, 1951, 584) in yields of 90—95%, and pentafluoroiodoethane from tetrafluoroethylene by Emeléus and Haszeldine's method (*J.*, 1949, 2948) in 85% yield.

Interaction of Pentafluoroiodoethane and Acetylene.—(a) *Under influence of heat.* Under optimum conditions, pentafluoroiodoethane (3·25 g.) was sealed with acetylene (0·41 g., 20% excess) in a Carius tube of 30-ml. capacity, and heated to 220—260° for 15—20 hours. A cuprene-type polymer was deposited on the walls of the vessel, and *ca.* 10% of the acetylene was found to be unchanged. The liquid products of reaction were shaken with mercury to remove iodine and distilled, to give 3 : 3 : 4 : 4 : 4-*pentafluoro*-1-*iodobut*-1-*ene* (2·60 g., 72%) (Found: C, 17·5; H, 0·7; F, 34·4; I, 46·4%; *M*, 274. $C_4H_2F_5I$ requires C, 17·6; H, 0·7; F, 34·9; I, 46·7%; *M*, 272), b. p. 84·4°, n_D^{25} 1·392. The higher-boiling products from several such experiments were combined and distilled, to give 5 : 5 : 6 : 6 : 6-*pentafluoro*-1-*iodohexa*-1 : 3-*diene* (*ca.* 0·5% yield) (Found: C, 23·6; H, 1·4; I, 41·7. $C_6H_4F_5I$ requires C, 24·2; H, 1·3; I, 42·6%), b. p. 104°/46 mm., *trans*-di-iodoethylene (0·5—1·0%) (Found: C, 9·0; H, 1·0. Calc. for $C_2H_2I_2$: C, 8·6; H, 0·7%), m. p. 72·5—73·5° after recrystallisation from ethanol (Keiser, *J. Amer. Chem. Soc.*, 1899, **21**, 265, reports m. p. 73°), and a fluorine-free oil, immiscible with, and sometimes contaminating, the fluoroiodohexadiene on distillation, which may be *cis*-di-iodoethylene.

(b) *Under influence of light.* Acetylene (1·55 g., 15% excess) and pentafluoroiodoethane (12·8 g.) were sealed in a series of Pyrex Carius tubes of 50-ml. capacity and irradiated at a distance of 12" by a Hanovia lamp without the Wood's filter. After 9 days the contents were combined and fractionated, to give unchanged acetylene (6%), unchanged pentafluoroiodoethane (3%), and higher-boiling material (13·0 g.), 57% of which was 3 : 3 : 4 : 4 : 4-pentafluoro-1-iodobutene.

Preparation of Pentafluorobutyne.—Dry, powdered potassium hydroxide (50 g.) was added to a 250-ml. flask fitted with a dropping-funnel and reflux water condenser leading to traps cooled in liquid air. After dropwise addition of a portion of the 3 : 3 : 4 : 4 : 4-pentafluoro-1-iodobut-1-ene (38·6 g.) to the flask, the temperature was slowly raised to 110°, then reduced to 70°, a further portion added, and the temperature raised to 110° again. After 5 hours no refluxing could be observed, and the contents of the flask were heated *in vacuo* to recover unchanged fluoroiodobutene (3·4 g., 9%). The volatile products of the dehydroiodination were purified by fractional condensation *in vacuo*, to give 3 : 3 : 4 : 4 : 4-*pentafluorobut*-1-*yne* (11·8 g., 63·5% based on fluoroiodobutene used) (Found: *M*, 144. C_4HF_5 requires *M*, 144). Its vapour pressure is represented over the temperature range −70° to −12° by the equation $\log P$ (mm.) = 7·5952 − 1231·7/*T*, whence the b. p. is calculated as −12°, the latent heat of vaporisation as 5640 cals./mole, and Trouton's constant as 21·6.

Copper, Silver, and Mercuric Pentafluorobutynylides.—By the method of Part IV (*J.*, 1951, 588), pentafluorobutyne (0·3—0·5 g.) was converted into the khaki-coloured *cuprous pentafluorobutynylide* (Found: Cu, 30·9. C_4F_5Cu requires Cu, 30·8%), the white *silver* analogue (Found: Ag, 42·8. C_4F_5Ag requires Ag, 43·1%), and the white, crystalline *mercuric* derivative (Found: C, 20·0; Hg, 41·2. $C_8F_{10}Hg$ requires C, 19·8; Hg, 41·2%), m. p. *ca.* 25° after sublimation at 100°/760 mm. The fluoro-alkyne was liberated quantitatively on heating of the acetylides with 5N-nitric acid.

Preparation of Trifluoropropyne.—(*a*) Trifluoroiodomethane was converted into trifluoropropyne by the method of Part IV in yields of 70%. (*b*) Route IV [6(*a*) and (*b*)] of Part V was modified as follows: Trifluoroiodomethane (0·33 mol.) was converted into 1 : 1 : 1-trifluoro-3-iodopropane (82% yield based on fluoro-iodide used) by reaction with ethylene (0·33 mol.) at 275° for 15 hours in a 300-ml. autoclave. The fluoroiodopropane (113 g., 0·51 mol.) was added dropwise during 2·5 hours to alcoholic potassium hydroxide (60 g., 1·1 mol., in 300 ml. of ethanol), and the evolved 3 : 3 : 3-trifluoropropene led into a 500-ml. silica flask containing bromine (103 g., 25% excess) and exposed to ultra-violet light. The excess of bromine was removed (sodium hydrogen sulphite) and the solution dried (P_4O_{10}); distillation gave 2 : 3-dibromo-1 : 1 : 1-trifluoropropane (120 g., 92·5%), b. p. 116°. To the stirred dibromide (110 g., 0·43 mol.), cooled to −5°, was slowly added ice-cold alcoholic potassium hydroxide (26 g., 0·46 mol., in 65 ml. of ethanol). Phenolphthalein was used to follow the course of reaction to avoid high local concentrations of alkali. After being stirred for 1 hour the reaction mixture was acidified (hydrochloric acid) and diluted with water to dissolve the potassium bromide, and the lower layer washed, dried (P_4O_{10}), and distilled, to give 2-bromo-3 : 3 : 3-trifluoroprop-1-ene (70·1 g., 91·5%), b. p. 33·8°. The volatile product formed during the dehydrohalogenation was 3 : 3 : 3-trifluoropropyne (0·2 g.). The bromotrifluoropropene (15·3 g., 0·09 mol.) was treated with bromine (16·5 g., 0·1 mol.) in a silica flask irradiated by ultra-violet light and fitted with a reflux condenser cooled to −78°, until no further refluxing was apparent. After cooling to 10°, the reaction mixture was treated with ice-cold alcoholic potassium hydroxide (5·6 g., 0·1 mol., in 15 ml. of ethanol) in the manner just described, and the lower layer after acidification was distilled, to give 1 : 2-dibromo-3 : 3 : 3-trifluoroprop-1-ene (17·8 g., 0·07 mol., 87%), b. p. 96°, and recovered 2-bromo-3 : 3 : 3-trifluoroprop-1-ene (1·22 g., 0·007 mol.). Dehalogenation of the 1 : 2-dibromo-3 : 3 : 3-trifluoropropene (17·8 g., 0·07 mol.) was effected by its addition during 5 hours to zinc (14 g.) in ethanol (60 ml.) at the reflux temperature; the yield of 3 : 3 : 3-trifluoropropyne was 93% (6·38 g., 0·068 mol.). The overall yield from 1 : 1 : 1-trifluoro-3-iodopropane was thus 70%.

Hydration of Trifluoropropyne.—(1) *In absence of a catalyst.* 3 : 3 : 3-Trifluoropropyne (1·14 g.) was sealed in a Carius tube with 10% sulphuric acid (5 ml.) and heated at 100° for 45 hours but was substantially unchanged.

(2) *In presence of mercuric sulphate.* (a) *Catalytic amounts.* 3 : 3 : 3-Trifluoropropyne (2·25 g., 0·024 mol.) was heated at 130° for 15 hours with mercuric sulphate (0·2 g., 0·0007 mol.). Mercury (0·096 g. ≡ 75% of the mercuric sulphate added) was liberated, 77% (1·74 g.) of the trifluoropropyne was recovered unchanged, and 1 : 1 : 1-trifluoroacetone (0·51 g., 19% yield, 84% based on acetylene used) (identified as described below) were formed. The aqueous

solution contained a trace of βββ-trifluoropropionic acid (see below), but 3 : 3 : 3-trifluoropropaldehyde could not be detected.

(b) *Excess of mercuric sulphate at room temperature.* The trifluoropropyne (1·05 g., 0·011 mol.) and mercuric sulphate (6·54 g., 0·022 mol.), shaken at room temperature for 148 hours with 15% sulphuric acid (5 ml.), gave unchanged trifluoropropyne (0·11 g., 10%), and a fraction *A* (Found: *M*, 113. Calc. for $C_3H_3OF_3$: *M*, 112). Carbon dioxide was not detected (see below). A 10% aliquot of fraction *A* gave a mixture of 2 : 4-dinitrophenylhydrazones melting over the range 125—128° and this could not be separated by fractional crystallisation on a micro-scale. The remainder of the gaseous fraction was shaken in a sealed tube for 24 hours with excess of a 2% aqueous dimedone solution, residual gaseous material *B* (*M*, 112) returned to the vacuum system, and the solid product removed by filtration. Treatment of the diluted, filtered aqueous solution from the hydration with an aqueous dimedone solution gave a small quantity of solid after 24 hours. The combined white solid was washed with water and recrystallised from aqueous ethanol, to give the *dimedone* derivative of 3 : 3 : 3-trifluoropropaldehyde (1·05 g.) (Found: C, 61·2; H, 6·5. $C_{19}H_{25}O_4F_3$ requires C, 61·0; H, 6·5%), m. p. 115°. The yield of 3 : 3 : 3-trifluoropropaldehyde was thus 28% based on the trifluoropropyne used.

A 20% aliquot of the gas *B* was treated for 24 hours with 2 : 4-dinitrophenylhydrazine. The solid formed was combined with a small amount arising by similar treatment of a 20% aliquot of the dimedone-treated hydration solution, and recrystallised from aqueous ethanol, to give the 2 : 4-dinitrophenylhydrazone of 1 : 1 : 1-trifluoroacetone (0·357 g.), m. p. 138—139° (see below). The yield of trifluoroacetone based on trifluoropropyne used was thus 61%, and the yields of aldehyde and ketone account for 89% of the fluoro-acetylene used.

The residual 80% aqueous aliquot was distilled, and the distillate extracted continuously by ether overnight. Tests for βββ-trifluoropropionic acid were negative. A small amount of mercury (<0·1 g.) had been liberated during the hydration.

(c) *Excess of mercuric sulphate at high temperatures.* 3 : 3 : 3-Trifluoropropyne (1·75 g., 0·019 mol.), mercuric sulphate (12·6 g.; 0·043 mol.), and 10% sulphuric acid (5 ml.) were heated in a Carius's tube at 135° for 15 hours to give: carbon dioxide (0·26 g., equiv. to 32% of trifluoropropyne), fluoroform (0·02 g.), and 1 : 1 : 1-trifluoroacetone (0·37 g., 18%) (Found: *M*, 114. Calc. for $C_3H_3OF_3$: *M*, 112), b. p. 22·0°. This gave a 2 : 4-dinitrophenylhydrazone (Found: N, 19·6. Calc. for $C_9H_7N_4O_4F_3$: N, 19·2%), m. p. 138·5—139·0°. Ultra-violet absorption in ethanol: $\lambda_{max.}$ 338, 256, and 218 mμ; ε 20,200, 11,700, and 13,050, respectively. Swarts (*Bull. Acad. roy. Belg.*, 1927, **13**, 175) reports b. p. 21·9° for the ketone, and Henne, Newman, Quill, and Staniforth (*J. Amer. Chem. Soc.*, 1947, **69**, 1819) report m. p. 139° for the 2 : 4-dinitrophenylhydrazone.

The filtered, pale brown aqueous solution was extracted by ether (50 ml.), and the extracts were dried ($MgSO_4$) and distilled, to give a pale yellow oil (0·52 g.) with an odour similar to that of the higher perfluoro-acids. Treatment of the oil with water gave an insoluble polymeric residue (*ca.* 0·1 g.) which was soluble in alcohol. A dimedone derivative could not be prepared before or after heating of the polymer with sodium carbonate solution. The water-soluble material was shown to be βββ-trifluoropropionic acid (*ca.* 22% yield): a specimen of the crude acid dissolved in ether and treated with an excess of an ethereal solution of *NN'*-bis-*p*-dimethylaminophenylcarbodi-imine (kindly given by Dr. H. G. Khorana) gave a precipitate, which was recrystallised from ethanol, giving *NN'-bis-p-dimethylaminophenyl-N-3 : 3 : 3-trifluoropropionylurea* (Found: N, 13·5. $C_{20}H_{23}N_4O_2F_3$ requires N, 13·7%), m. p. 155°, identical in m. p. and infra-red spectrum with the derivative prepared from a known specimen of βββ-trifluoropropionic acid. An aqueous solution of the crude βββ-trifluoropropionic acid was also added in slight excess to a 6% solution of nitron in 10% acetic acid to give the *βββ-trifluoropropionate* (Found: N, 12·9. $C_{23}H_{19}N_4O_2F_3$ requires N, 12·7%) as an off-white solid, recrystallised from aqueous ethanol and characterised by its infra-red spectrum. The aqueous solution of crude βββ-trifluoropropionic acid gave a negative test for aldehyde.

A similar experiment with the trifluoropropyne (2·2 g., 0·023 mol.), mercuric sulphate (7·86 g., 0·027 mol.), and 10% sulphuric acid (5 ml.), heated at 140° for 15 hours, gave a 16% yield of trifluoroacetone.

Hydration of Pentafluorobutyne.—No reaction was detected when the pentafluorobutyne (2·4 g.) was shaken with 10% sulphuric acid (5 ml.) at 110° for 28 hours, but pentafluorobutyne (4·33 g., 0·03 mol.), mercuric sulphate (16·6 g., 0·056 mol.), and 10% sulphuric acid (5 ml.), heated at 110° for 16 hours, gave carbon dioxide (0·14 g.; equiv. to 13% of the butyne), unchanged fluoro-acetylene (0·07 g.; 16%), pentafluoroethane (0·07 g.) (Found: *M*, 121. Calc. for C_2HF_5: *M*, 120) (identified by its infra-red spectrum), and 3 : 3 : 4 : 4 : 4-*pentafluoro-*

butan-2-one (0·78 g., 16%) (Found : *M*, 162. $C_4H_3OF_5$ requires *M*, 162), b. p. 39·5—40°. This ketone readily formed a hydrate which could be reconverted into the ketone by distillation from phosphoric oxide.

The 2 : 4-*dinitrophenylhydrazone* (Found : N, 16·0. $C_{10}H_7O_4N_4F_5$ requires N, 16·4%), m. p. 99°, was recrystallised from aqueous ethanol, and had absorption maxima in ethanol at 336, 256, and 220 mμ (ε 20,100, 11,600, and 12,900, respectively). The ketone and the 2 : 4-dinitrophenylhydrazone were further characterised by their infra-red spectra.

Ether-extraction of the aqueous phase from the hydration gave crude ββγγγ-pentafluorobutyric acid (*ca.* 1·4 g., 17%), which with an ethereal solution of *NN'*-bis-*p*-dimethylaminophenylcarbodi-imine gave the corresponding urea as a white solid, m. p. 151°, characterised by its infra-red spectrum.

One of us (K. L.) expresses his appreciation to Imperial Chemical Industries Limited, General Chemicals, Widnes, and to Courtauld's Scientific and Educational Trust for grants during the tenure of which this work was carried out.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, March 1st*, 1952.]

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669. *Reactions of Fluorocarbon Radicals. Part VII.* Addition to Trifluoromethyl-substituted Acetylenes.†*

By R. N. HASZELDINE.

The addition of HX to 3 : 3 : 3-trifluoropropyne and hexafluorobut-2-yne yields $CF_3{\cdot}CH{:}CHX$ (X = F, Cl, Br, I, CN, OMe, OEt, NEt_2) and $CF_3{\cdot}CH{:}CX{\cdot}CF_3$ (X = Cl, Br, OMe, OEt, NEt_2). Addition tends to stop at this stage, but under more stringent conditions $CF_3{\cdot}CH_2{\cdot}CHX_2$ and $CF_3{\cdot}CH_2{\cdot}CX_2{\cdot}CF_3$ (X = OMe, OEt) are formed. Hydrogenolysis of the vinylic ethers $CF_3{\cdot}CH{:}CH{\cdot}OR$ and $CF_3{\cdot}CH{:}C(OR){\cdot}CF_3$ or hydrolysis of the dialkoxy-compounds $CF_3{\cdot}CH_2{\cdot}CH(OR)_2$ and $CF_3{\cdot}CH_2{\cdot}C(OR)_2{\cdot}CF_3$ yields βββ-trifluoropropaldehyde and hexafluorobut-2-one. Hydrolysis of 1-cyano-3 : 3 : 3-trifluoropropene gives γγγ-trifluorocrotonic acid, independently synthesised by the interaction of trifluoroiodomethane and acrylonitrile followed by treatment with alkali. The addition of hydrogen bromide in ultra-violet light to trifluoropropyne and hexafluorobut-2-yne is reported.

The importance of hyperconjugated structures of the type $F{-}CF_2{:}C{:}C<$ in olefinic and acetylenic fluorine compounds is discussed.

As part of a general study of the influence of perfluoroalkyl groups on the properties of adjacent organic functional groups, an investigation has been made of ionic and free-radical addition reactions to 3 : 3 : 3-trifluoropropyne and to hexafluorobut-2-yne, compounds in which the functional group is $-C{\equiv}C-$. When X = F, Cl, Br, I, addition of HX to trifluoropropyne gave $CF_3{\cdot}CH{:}CHX$, *i.e.*, addition was opposite to that in propyne. The reaction when X = F, Cl, or Br took place smoothly and without catalysts; the addition of hydrogen chloride and bromide was particularly rapid. Use of an excess of hydrogen halide did not bring about the addition of 2 mols. under moderate conditions. Boron trifluoride (when X = F) or aluminium halides (X = Cl or Br) catalysed the addition reactions, and the addition of hydrogen bromide, for example, could thereby be brought about at a lower temperature. The use of aluminium tri-iodide was necessary to effect addition of hydrogen iodide at room temperature. At higher temperatures, and in presence of an excess of hydrogen iodide, were obtained aluminium fluoride, 3 : 3 : 3-trifluoro-1-iodopropene, 3 : 3 : 3-trifluoropropene, and unidentified higher-boiling products. The

* Part VI, preceding paper.

† Part of a paper presented in abstract at 120th Meeting of the American Chemical Society, Sept. 1951.

formation of the trifluoropropene may be attributed to the reduction of 3 : 3 : 3-trifluoro-1-iodopropene or, less probably, to elimination of iodine from a di-iodide :

$$CF_3{\cdot}C{\equiv}CH \xrightarrow[AlI_3]{HI} CF_3{\cdot}CH{:}CHI \begin{cases} \xrightarrow{HI} CF_3{\cdot}CH{:}CH_2 \\ \xrightarrow{AlI_3} CF_3{\cdot}CHI{\cdot}CH_2I \xrightarrow{-I_2} CF_3{\cdot}CH{:}CH_2 \end{cases}$$

Addition of iodine to 3 : 3 : 3-trifluoropropene to give a stable di-iodide could not be achieved.

The addition of hydrogen bromide under the influence of ultra-violet radiation was carried out with conditions such that the ionic reaction could not occur; the product was exclusively 1-bromo-3 : 3 : 3-trifluoropropene. Trifluoropropyne thus yields the same product from the ionic or the free-radical addition of hydrogen bromide.

The addition of hydrogen cyanide to trifluoropropyne was slow with the temperature and catalyst used, but a satisfactory yield of γγγ-trifluorocrotonic acid was obtained by hydrolysis of the addition product. The structure of the fluorocrotonic acid is supported by its infra-red spectrum. Thermal decomposition of the sodium salt of the acid in ethylene glycol containing boric acid gave the expected 3 : 3 : 3-trifluoropropene, but even when the olefin was removed from the reaction medium as rapidly as possible, appreciable attack on the allylic trifluoromethyl group was apparent. Application of the simultaneous iodination and decarboxylation technique (Haszeldine, *J.*, 1951, 584) to silver γγγ-trifluorocrotonate yielded exclusively 3 : 3 : 3-trifluoro-1-iodopropene, $CF_3{\cdot}CH{:}CH{\cdot}CO_2Ag \xrightarrow{I_2} CF_3{\cdot}CH{:}CHI + CO_2 + AgI$, thereby eliminating the possibility of formation of 2-cyano-3 : 3 : 3-trifluoropropene by the interaction of trifluoropropyne and hydrogen cyanide.

An independent synthesis of γγγ-trifluorocrotonic acid was made by the addition of trifluoroiodomethane to acrylonitrile under the influence of ultra-violet light, followed by dehydroiodination and hydrolysis of the iodonitrile :

$$CF_3I + CH_2{:}CHCN \xrightarrow{h\nu} CF_3{\cdot}CH_2{\cdot}CHI{\cdot}CN \xrightarrow{\text{alc. KOH}} CF_3{\cdot}CH{:}CH{\cdot}CO_2H$$

The photochemical addition reaction probably proceeds by the free-radical chain mechanism (Haszeldine, *J.*, 1949, 2856; 1950, 2037; preceding paper; Haszeldine and Steele, *Chem. and Ind.*, 1951, 684), *viz.*,

$$CF_3I \xrightarrow{h\nu} CF_3{\cdot} + {\cdot}I$$
$$CF_3{\cdot} + CH_2{:}CH{\cdot}CN \longrightarrow CF_3{\cdot}CH_2{\cdot}\dot{C}H{\cdot}CN$$
$$CF_3{\cdot}CH_2{\cdot}\dot{C}H{\cdot}CN + CF_3I \longrightarrow CF_3{\cdot}CH_2{\cdot}CHI{\cdot}CN + CF_3{\cdot}, \text{ etc.}$$

Treatment of trifluoropropyne with methyl or ethyl alcohol in the presence of the corresponding alkoxide yields the 1-alkoxy-3 : 3 : 3-trifluoropropenes by nucleophilic attack, *e.g.*,

$$MeO^- + CF_3{\cdot}C{\equiv}CH \longrightarrow CF_3{\cdot}\bar{C}{:}CH{\cdot}OMe$$
$$CF_3{\cdot}\bar{C}{:}CH{\cdot}OMe + MeOH \longrightarrow CF_3{\cdot}CH{:}CH{\cdot}OMe + MeO^-$$

The structures of the vinylic ethers were proved by treatment with hydrogen under pressure in presence of Raney nickel: partial hydrogenation to the known 1-alkoxy-3 : 3 : 3-trifluoropropanes occurred, but the main reaction was hydrogenolysis to methane or ethane and 3 : 3 : 3-trifluoropropaldehyde :

$$CF_3{\cdot}CH{:}CH{\cdot}OR \xrightarrow{[H]} CF_3{\cdot}CH_2{\cdot}CHO + RH + CF_3{\cdot}CH_2{\cdot}CH_2{\cdot}OR$$

The aldehyde was identified and estimated as its 2 : 4-dinitrophenylhydrazone, and the absence of trifluoroacetone was shown by removal of the aldehyde as the dimedone derivative followed by testing with 2 : 4-dinitrophenylhydrazine. The absence of trifluoroacetone and of the known isomeric 2-ethoxy-3 : 3 : 3-trifluoropropane, whose boiling

point differs appreciably from that of the 1-ethoxy-compound, proved that the alternative reaction

$$CF_3{\cdot}C{\equiv}CH + R{\cdot}OH \longrightarrow CF_3{\cdot}C(OR){:}CH_2 \xrightarrow{[H]} CF_3{\cdot}CO{\cdot}CH_3 + RH + CF_3{\cdot}CH(OR){\cdot}CH_3$$

did not occur. The 1-alkoxy-3 : 3 : 3-trifluoropropenes gave ββ-trifluoropropaldehyde and the alkyl iodide on treatment with hydriodic acid, and trifluoroacetone could not be detected.

As with the addition of hydrogen halide, the addition of the alcohols tended to stop with the formation of the vinyl compound, even in the presence of excess of alcohol. The addition of a second mol. of an alcohol was effected at higher temperatures, but was accompanied by appreciable conversion of the trifluoromethyl groups into fluoride. The dialkoxy-compound was not isolated in the pure state but was immediately hydrolysed with sulphuric acid to give only 3 : 3 : 3-trifluoropropaldehyde, the formation of which proves that the addition of the second mol. of alcohol gave 1 : 1-diethoxy-3 : 3 : 3-trifluoropropane. By a similar nucleophilic attack on trifluoropropyne was obtained a moderate yield of 1-diethylamino-3 : 3 : 3-trifluoropropene; the direction of addition was assumed by analogy with the alcohol addition reactions. An unidentified by-product from the interaction of trifluoropropyne and diethylamine contained a triple bond, and by analogy with the work of Rose and Gale (*J.*, 1949, 793) on phenylacetylene may be formed as follows :

$$CF_3{\cdot}CH{:}CH{\cdot}NEt_2 \xrightarrow{CF_3{\cdot}C{\equiv}CH} CF_3{\cdot}CH_2{\cdot}CH(NEt_2){\cdot}C{\equiv}C{\cdot}CF_3$$

The reaction of hydrogen halide (X = Cl, Br) with hexafluorobut-2-yne was slow in the absence of an aluminium halide catalyst. In both cases addition tended to stop at the 2-halogeno-1 : 1 : 1 : 4 : 4 : 4-hexafluorobut-2-ene stage even in the presence of excess of hydrogen halide; aluminium fluoride was also formed, and it is possible that this may be the active catalyst. By contrast, the photochemical addition of hydrogen bromide was rapid and almost quantitative. Reaction again stopped at the 2-bromohexafluorobut-2-ene stage, and the only by-product was 2 : 3-dibromohexafluorobut-2-ene. There was no reaction between hydrogen bromide and hexafluorobut-2-yne in the dark.

Although the aluminium halide-catalysed addition of hydrogen halide was slow, nucleophilic attack on hexafluorobut-2-yne occurs very readily. The addition of both methanol and ethanol in presence of their respective alkoxides took place below 0° and yielded the vinyl ethers. Fluoride was again formed by attack on the trifluoromethyl groups. A recent patent by Chaney (*Chem. Abs.*, 1951, **45**, 2015) also describes the addition of ethanol to hexafluorobut-2-yne.

The vinyl ethers yielded trifluoroacetic acid on oxidation and gave dibromides. The ethyl ether underwent catalytic hydrogenolysis :

$$CF_3{\cdot}CH{:}C(OEt){\cdot}CF_3 \xrightarrow{[H]} C_2H_6 + CF_3{\cdot}CH_2{\cdot}CO{\cdot}CF_3$$

at higher temperatures than required for 1-ethoxy-3 : 3 : 3-trifluoropropene, but the formation of the hydrogenated ether was not observed. The ketone was also formed by the interaction of the 2-alkoxy-1 : 1 : 1 : 4 : 4 : 4-hexafluorobutenes and hydriodic acid.

Addition of methanol or ethanol to the 2-alkoxyhexafluorobut-2-enes was achieved more readily than with the corresponding alkoxytrifluoropropene, and yielded the 2 : 2-dialkoxyhexafluorobutanes, small amounts of which were obtained during the initial formation of the 2-alkoxyhexafluorobutenes from hexafluorobutyne. The direction of addition of the second molecule of alcohol was proved by the formation of 1 : 1 : 1 : 4 : 4 : 4-hexafluorobutan-2-one on treatment of the dialkoxy-compounds with sulphuric acid :

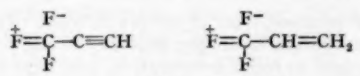
$$CF_3{\cdot}CH_2{\cdot}C(OR)_2{\cdot}CF_3 \longrightarrow CF_3{\cdot}CH_2{\cdot}CO{\cdot}CF_3$$

This route is more convenient than the original procedure for the butanone (Henne, Schmitz, and Finnegan, *J. Amer. Chem. Soc.*, 1950, **72**, 4195).

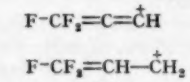
Secondary amines also undergo ready reaction with hexafluorobut-2-yne; *e.g.*, diethylamine gave 2-diethylaminohexafluorobut-2-ene, $CF_3{\cdot}CH{:}C(NEt_2){\cdot}CF_3$, and the addition of a second mol. of the amine could not be effected under moderate conditions.

Discussion.—The addition of HX to trifluoropropyne to give exclusively $CF_3 \cdot CH{:}CHX$ indicates that the polarisation of the alkyne molecule during ionic reactions is $F_3C \leftarrow C \equiv CH$. The reversal of polarisation compared with that of propyne is similar to that for 3 : 3 : 3-trifluoropropene, deduced from the direction of addition of hydrogen fluoride, chloride, and bromide and of alcohols (unpublished data; see also Henne and Kaye, *ibid.*, p. 3369).

Two main effects must be distinguished in considering the effect of a trifluoromethyl group on an adjacent unsaturated group such as $-C \equiv CH$ or $-CH{:}CH_2$, *viz.*, (*a*) the powerful inductive effect of the trifluoromethyl group, which may be deduced from the fact that trifluoroacetic acid is appreciably stronger than trichloroacetic acid, and (*b*) resonance effects. Concerning (*b*), double-bonded structures of type (I) affect only the trifluoromethyl group, but hyperconjugation (no-bond resonance) structures of type (II) involve the unsaturated system, and it is considered that, owing to the extreme negativity of fluorine, such resonance structures make a much greater contribution to the real resonance level than do hyperconjugation structures in hydrocarbon compounds (*e.g.*, $H^+CH_2{:}C{:}\bar{C}H$). Although the inductive and hyperconjugation effects often act in the same direction concerning reactions involving addition to the unsaturated linkage (*e.g.*, with trifluoropropyne), the possible importance of hyperconjugation effects in the interpretation of the reactions of organic fluorine compounds does not seem to have been fully appreciated.



(I)

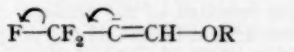


(II)

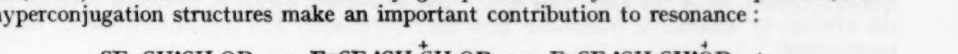
The trifluoromethyl group exerts a marked immobilising or deactivating effect on the unsaturation electrons of the adjacent double or triple bonds towards electrophilic attack; the (assumed) electrophilic additions of hydrogen chloride or bromide to trifluoropropyne proceed readily in absence of a catalyst, but qualitatively are slower than with propyne. The use of aluminium halides is not essential (as with 3 : 3 : 3-trifluoropropene) to bring about reaction. The increased deactivation to electrophilic attack in hexafluorobut-2-yne is revealed by the necessity to use a catalyst to effect addition of hydrogen chloride or bromide at moderate temperatures. Only the mono-addition product is formed from trifluoropropyne and hexafluorobut-2-yne in presence of excess of hydrogen halide, and it is evident that the trifluoromethyl groups deactivate the double bond more than the triple bond towards electrophilic attack.

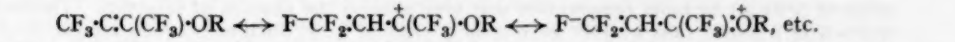
Decreased activity to electrophilic attack is accompanied by increased susceptibility to nucleophilic attack, and the reactions of alcohols or of amines with the triple bond in the perfluoroalkylacetylenes occur almost as readily as with the polyfluoro-olefins such as tetrafluoroethylene or chlorotrifluoroethylene. The reactions tend to stop with the formation of the mono-addition compound, again indicating the greater influence of trifluoromethyl groups on double compared with triple bonds.

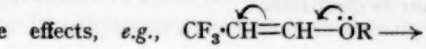
The formation of fluoride ion during reaction may occur by direct attack on the trifluoromethyl groups of the alkynes, or by loss of fluoride from the intermediate ion



in a manner outlined earlier for perfluoroalkyl carbanions (Haszeldine, *Nature*, 1951, **168**, 1028). Attack on the trifluoromethyl groups of the vinyl ethers is also possible, since hyperconjugation structures make an important contribution to resonance:





The addition of the second molecule of alcohol gives the products expected from the above effects, *e.g.*,  . Qualitatively, base-

catalysed addition of one and two molecules of an alcohol, or of one molecule of diethylamine, takes place more readily with hexafluorobutyne than with trifluoropropyne, presumably because of the increased electron withdrawal from the unsaturated link.

The hydrogenolysis which occurs with the vinyl ethers is similar to that observed with compounds of the type R·CO·CR:CH·OEt (R, aromatic or aliphatic) (Kötz and Schaeffer, *J. pr. Chem.*, **1913**, **196**, 604; Baker and Weiss, *J. Amer. Chem. Soc.*, **1944**, **66**, 343; Baker and Schlesinger, *ibid.*, **1946**, **68**, 2009). Although hydrogenation accompanies hydrogenolysis in the case of 1-alkoxy-3 : 3 : 3-trifluoropropene, the reaction does not proceed *via* the 1-alkoxy-3 : 3 : 3-trifluoropropane, since this was shown to be stable under the conditions used. Furthermore, the ready hydrogenolysis cannot be correlated completely with the electron drain from the oxygen by the effects outlined earlier, since hydrogenolysis of 2-ethoxy-1 : 1 : 1 : 4 : 4 : 4-hexafluorobutene is more difficult and is not accompanied by hydrogenation.

Experimental

Preparation of Trifluoropropyne and Hexafluorobut-2-yne.—Trifluoropropyne was prepared from trifluoroiodomethane by the methods of Parts IV and V (*locc. cit.*). Hexafluorobut-2-yne was obtained from the addition product of trifluoroiodomethane and 3 : 3 : 3-trifluoropropene, by the bromination, dehydrobromination, and debromination sequence described by Haszeldine (*J.*, 1952, 2504). Unless otherwise stated, reactions were carried out in sealed Pyrex tubes of *ca.* 50 ml. capacity.

Addition of Hydrogen Halides to Trifluoropropyne.—(a) *Hydrogen fluoride.* Into a cooled nickel bomb of 30-ml. capacity was distilled anhydrous hydrogen fluoride (10 ml.) and trifluoropropyne (0·94 g.). The bomb was sealed, warmed to room temperature, and kept for 48 hours, the temperature then being raised to 60° for 4 hours. After cooling, the reaction products were distilled into water, and the residual volatile material condensed, washed with water, and transferred to a vacuum system. Fractionation gave 1 : 3 : 3 : 3-*tetrafluoroprop*-1-*ene* (1·05 g., 92%) (Found: C, 31·8; H, 2·2%; *M*, 114. $C_3H_3F_4$ requires C, 31·6; H, 1·75%; *M*, 114), b. p. −16°. The structure of this compound is known by independent synthesis from vinyl fluoride and trifluoroiodomethane followed by dehydroiodination (Steele, unpublished results). Use of boron trifluoride as catalyst brought about the addition reaction at a lower temperature.

(b) *Hydrogen chloride.* Pure dry hydrogen chloride (0·38 g.) was condensed into a Pyrex Carius tube of 50-ml. capacity containing trifluoropropyne (0·94 g.). On warming to room temperature an immediate reaction was apparent, and after 2 hours the tube was opened and the contents were fractionated *in vacuo* to give hydrogen chloride (0·01 g.) and 1-chloro-3 : 3 : 3-trifluoropropene (1·30 g., 100%) (Found: *M*, 130·5. Calc. for $C_3H_2ClF_3$: *M*, 130·5), b. p. 21°. The b. p. reported in Part V (*loc. cit.*) was 21°, and the b. p. of 2-chloro-3 : 3 : 3-trifluoropropene was 14—15°. Use of a 100% excess of hydrogen chloride at room temperature gave only 1-chloro-3 : 3 : 3-trifluoropropene, and a dichloro-compound could not be detected.

(c) *Hydrogen bromide.* Anhydrous hydrogen bromide (0·82 g.) and trifluoropropyne (0·94 g.) were condensed in a Carius tube. No reaction was observed after 4 hours below −15° (cf. the photochemical addition, below), but after 2 hours at 0° complete reaction had occurred and no unchanged trifluoropropyne was detected. The product of reaction was exclusively 1-bromo-3 : 3 : 3-trifluoropropene (1·75 g., 100%) (Found: *M*, 174. Calc. for $C_3H_2BrF_3$: *M*, 175), b. p. 40°. The b. p.s of 1-bromo- and 2-bromo-3 : 3 : 3-trifluoropropene are 41° and 33·5° (Part V, *loc. cit.*).

The above experiment was repeated in the presence of aluminium tribromide (0·1 g.) at −25°. Reaction was complete after 4 hours and the product was again exclusively 1-bromo-3 : 3 : 3-trifluoropropene (91% yield). A control experiment showed that aluminium tribromide did not bring about rearrangement of 3 : 3 : 3-trifluoropropene or of 1-bromo-3 : 3 : 3-trifluoropropene under the conditions used. Use of a 300% excess of hydrogen bromide in the absence of aluminium tribromide gave only 1-bromo-3 : 3 : 3-trifluoropropene at room temperature.

(d) *Hydrogen iodide.* The interaction of anhydrous hydrogen iodide (1·38 g.) and trifluoropropyne (0·94 g.) at room temperature was very slow in the absence of catalysts. Thermal reaction in a sealed tube at 100° gave a 65% yield of 3 : 3 : 3-trifluoro-1-iodopropene, b. p. 70—71°. Additional material boiling over the range 67—74° was also obtained, however, and could not be resolved into definite fractions by distillation.

When the experiment was repeated in the presence of aluminium tri-iodide (0·25 g.), steady

reaction took place at room temperature and, after 24 hours, fractionation gave trifluoropropyne (17%), hydrogen iodide (19%), and a clean-cut fraction (1·74 g., 80%) of 3 : 3 : 3-trifluoro-1-iodopropene, b. p. 70·5°. The b. p. of this compound recorded in Part II (Haszeldine, *J.*, 1950, 3037) was 70·2°, and since the b. p. of the isomeric 3 : 3 : 3-trifluoro-2-iodopropene is unknown, identity was confirmed by comparison of infra-red spectra.

A similar experiment using a 100% excess of hydrogen iodide at 100° in the presence of aluminium tri-iodide gave 3 : 3 : 3-trifluoro-1-iodopropene (20%), 3 : 3 : 3-trifluoropropene (8%), unidentified higher-boiling material containing free iodine, aluminium trifluoride, and unchanged aluminium tri-iodide.

Addition of Hydrogen Cyanide to Trifluoropropyne.—Trifluoropropyne (0·94 g.) was sealed in a Carius tube with anhydrous hydrogen cyanide (0·81 g.), potassium cyanide (0·1 g.), potassium chloride (0·2 g.), cuprous chloride (0·8 g.), and water (10 ml.), and heated to 110° for 24 hours. Unchanged trifluoropropyne (48%) was recovered. A similar experiment carried out at 120° for 36 hours gave 36% recovered trifluoropropyne. The combined liquid phase was filtered through glass-wool, treated with an excess of 10% sodium hydroxide solution, and slowly heated under reflux to 80°. After filtration the solution was acidified (sulphuric acid) and continuously extracted by ether for 24 hours. After drying (Na_2SO_4), the ether was removed and the residual solid was fractionally recrystallised from light petroleum to give *γγγ-trifluorocrotonic acid* (1·01 g., 62%) (Found: C, 34·1; H, 2·3%; equiv., 140. $C_4H_3O_2F_3$ requires C, 34·3; H, 2·1%; equiv., 140), m. p. 51°.

The infra-red spectrum of γγγ-trifluorocrotonic acid shows a sharp band at 3·26 μ due to the vinylic hydrogen atoms, and strong bands at 7·67, 7·87, and 8·76 μ attributed to carbon–fluorine stretching vibrations. The *trans* ·CH:CH· group is revealed by bands at 6·00 and 10·28 μ (cf. Haszeldine, *Nature*, 1951, **168**, 1025; *J.*, 1952, 2504), and the carboxyl group produces bands at 3·85 μ (bonded OH group), 5·85 μ (C=O) and 5·93 μ (dimer). Corresponding bands in crotonic acid are 6·06 and 10·31 μ (·CH:CH·) and 3·85 and 5·85 μ (CO_2H). Other strong bands in the spectrum of trifluorocrotonic acid are at 10·8, 11·54, 13·98, and 14·10 μ.

Decarboxylation of γγγ-Trifluorocrotonic Acid.—(a) *Of the sodium salt.* The fluorocrotonic acid was converted into its sodium salt (0·40 g.), which was placed in a flask containing ethylene glycol (15 ml.) and boric acid (2 g.) (cf. Auerbach, Verhoek, and Henne, *J. Amer. Chem. Soc.*, 1950, **72**, 299) and fitted with a reflux condenser leading to traps cooled by liquid air. The temperature was raised from 150° to 200° during 4 hours, and by controlled pumping a vigorous reflux was maintained and the volatile products of reaction removed from the reaction vessel. These were then passed through 15% sodium hydroxide, and the residual gas, dried by distillation *in vacuo*, was found to be 3 : 3 : 3-trifluoropropene (0·99 g., 41%).

(b) *Of the silver salt by iodine.* The silver salt (1·23 g.), prepared from the acid by treatment with silver oxide and carbonate, was dried *in vacuo* and mixed with dry powdered iodine (3 g.). The mixture was then rapidly heated in a silica trap at a pressure of *ca.* 10 mm., so that the reaction products collected in an adjacent trap cooled in liquid air. After removal of the carbon dioxide by allowing the trap to warm to room temperature, the excess of iodine was removed by treatment with thiosulphate, and the liquid distilled to give only 3 : 3 : 3-trifluoro-1-iodopropene (0·83 g., 76%). The absence of isomers was shown by examination of the infra-red spectrum.

Alternative Synthesis of γγγ-Trifluorocrotonic Acid.—Acrylonitrile (0·53 g.) was sealed with excess of trifluoroiodomethane (8·5 g.) in a Pyrex tube which was then irradiated by ultra-violet light for 48 hours. The excess of trifluoroiodomethane was removed, and unchanged acrylonitrile (*ca.* 0·01 g.) was distilled from the residual liquid *in vacuo*. The γγγ-trifluoro-α-iodobutyronitrile was not isolated in the pure state but was separated from a trace of poly(acrylonitrile) by semimicro-distillation *in vacuo*, and treated immediately with a 5% excess of 10% alcoholic potassium hydroxide, initially at room temperature and finally at 50° for 1 hour. After acidification with excess of dilute sulphuric acid, ether extraction followed by crystallisation from light petroleum gave γγγ-trifluorocrotonic acid (1·02 g., 72%), m. p. 50·5—51°.

There was no reaction between trifluoroiodomethane and acrylonitrile in the absence of light.

Photochemical Addition of Hydrogen Bromide.—Hydrogen bromide (0·82 g.) and trifluoropropyne (0·94 g.) were sealed *in vacuo* in a carefully cleaned Pyrex test-tube which was then allowed to warm to −60° at which temperature it was maintained by partly surrounding the reaction vessel by solid carbon dioxide. After 36 hours in the dark the contents of the tube were transferred to a vacuum system without allowing the temperature to rise above −40°; fractionation *in vacuo* showed that no reaction had occurred.

The experiment was repeated in the same vessel but with irradiation from a Hanovia ultra-violet lamp at a distance of 2 ft. The temperature was kept at $-60° \pm 5°$ throughout, and after 8 hours the reaction tube was immersed in a bath at $-40°$, opened, and the volatile reaction products removed by pumping; only a trace of hydrogen bromide was found, and distillation of the product with b. p. $>0°$ showed it to be exclusively 1-bromo-3 : 3 : 3-trifluoropropene, b. p. 39·5—40°, n_D^{20} 1·357 (see above). A second control experiment was then made in the same tube at $-60°$ and confirmed the absence of reaction in the dark.

Addition of Methanol and Ethanol to Trifluoropropyne.—A Carius tube of 100-ml. capacity was charged with methanol (25 ml.) and sodium (0·5 g.) and, after completion of reaction, was cooled in liquid air. Trifluoropropyne (1·88 g.) was then added, and the tube sealed *in vacuo*. When the tube was allowed to warm, reaction became apparent at *ca.* $-20°$, and this temperature was therefore maintained for 3 hours, after which no unchanged trifluoropropyne could be recovered. The contents of the tube were treated with water (20 ml.) and then dilute hydrochloric acid until almost neutral. The lower layer was then removed, washed with water, dried (P_2O_5), and distilled to give 3 : 3 : 3-*trifluoro*-1-*methoxypropene* (2·32 g., 92%) (Found: C, 38·0%; *M*, 124. $C_4H_5OF_3$ requires C, 38·1%; *M*, 126), b. p. 83—84°. A test for fluoride on the aqueous solution was positive.

A similar experiment with ethanol instead of methanol at $-5°$ to $-10°$ gave 1-*ethoxy*-3 : 3 : 3-*trifluoropropene* (2·55 g.; 91%) (Found: C, 42·6%; *M*, 138. $C_5H_7OF_3$ requires C, 42·9%; *M*, 140), b. p. 103°, n_D^{25} 1·349. A. L. Henne and M. Nager have independently obtained this compound by a similar route (personal communication).

The alkoxy-3 : 3 : 3-trifluoropropenes gave a positive unsaturation test with potassium permanganate, and on oxidation with alkaline permanganate afforded trifluoroacetic acid, characterised as its amide, in yields of 58 and 62%. The compounds absorbed bromine to give higher-boiling liquids which were not characterised further.

When heated under reflux with an excess of constant-boiling hydriodic acid, 1-methoxy- and 1-ethoxy-3 : 3 : 3-trifluoropropene (0·71 g.; 0·81 g.) gave 57 and 61% yields of βββ-trifluoropropaldehyde; methyl and ethyl iodide were also formed.

Hydrogenation of 1-*Alkoxy*-3 : 3 : 3-*trifluoropropenes.*—A series of Carius tubes were charged with 3 : 3 : 3-trifluoro-1-methoxypropene (1·25 g.), hydrogen (0·1 g.), Raney nickel (0·3 g.), and ethanol (4 ml.), and were heated to 10—15° for 1 hour. The volatile products were found to be methane (80% of theory) (Found: *M*, 16. Calc. for CH_4: *M*, 16) and hydrogen. The contents of the tubes were poured into water (30 ml.) and filtered, and a small lower layer was removed and examined later. The aqueous solution showed positive tests for an aldehyde, which was shown to be βββ-trifluoropropaldehyde (79% yield) by formation of its 2 : 4-dinitrophenylhydrazone, m. p. 150·5—151°, mixed m. p. 150—151°. Henne, Pelley, and Alm (*J. Amer. Chem. Soc.*, 1950, **72**, 3370) report m. p. 150—151°.

The experiment was repeated under the same conditions and the yield of 3 : 3 : 3-trifluoropropaldehyde (82%) was estimated by formation of its dimedone, m. p. 114° (Part VI, *loc. cit.*). Treatment of the solution after dimedone formation with 2 : 4-dinitrophenylhydrazine gave only a trace of the 2 : 4-dinitrophenylhydrazone of the aldehyde, m. p. 150°, and no evidence for the 2 : 4-dinitrophenylhydrazone of 1 : 1 : 1-trifluoroacetone (m. p. 138—139°). The lower layer obtained on pouring the filtered hydrogenation mixture into water was combined with that from the first experiment, washed, dried, and distilled to give 3 : 3 : 3-trifluoro-1-methoxypropane (15% yield) (Found: C, 37·9%; *M*, 128. Calc. for $C_4H_7OF_3$: C, 37·5%; *M*, 128), b. p. 54·5—55·5°. Henne and Smook (*J. Amer. Chem. Soc.*, 1950, **72**, 4378) report b. p. 54·8°.

The hydrogenation of 3 : 3 : 3-trifluoro-1-methoxypropene (1·25 g.) in a small autoclave under 10 atm. of hydrogen and with freshly-prepared Raney nickel gave a theoretical yield of methane; the yield of 3 : 3 : 3-trifluoropropaldehyde was 91%.

Under similar conditions in an autoclave, 1-ethoxy-3 : 3 : 3-trifluoropropene (1·41 g.) gave a 98% yield of ethane (Found: *M*, 30. Calc. for C_2H_6: *M*, 30) and an 89% yield of trifluoropropaldehyde. The reaction of the ether (2·31 g. total) with hydrogen in sealed tubes by the method described above but with methanol as solvent gave ethane (78%), 3 : 3 : 3-trifluoropropaldehyde (74%), and 1-ethoxy-3 : 3 : 3-trifluoropropane (18%) (Found: C, 42·0%; *M*, 140. Calc. for $C_5H_9OF_3$: C, 42·3%; *M*, 142), b. p. 72—73·5°. Henne and Smook (*loc. cit.*) report b. p. 72·2° for the last compound and 63—64° for the isomeric 2-ethoxy-3 : 3 : 3-trifluoropropane. The yield of 3 : 3 : 3-trifluoropropaldehyde was estimated by 2 : 4-dinitrophenylhydrazone formation from an aliquot and the absence of 1 : 1 : 1-trifluoroacetone was shown by tests with 2 : 4-dinitrophenylhydrazine solution after precipitation of the dimedone derivative.

Under identical conditions, 1-methoxy- and 1-ethoxy-3 : 3 : 3-trifluoropropane showed no reaction with hydrogen and Raney nickel.

Addition of Ethanol to 1-Ethoxy-3 : 3 : 3-trifluoropropene.—(i) There was no indication of the addition of 2 mols. of ethanol to trifluoropropyne at 0° in the presence of sodium ethoxide, even after 7 days. (ii) To pure 1-ethoxy-3 : 3 : 3-trifluoropropene (1·70 g.) was added ethanol (25 ml.) containing sodium ethoxide (4 g.), and the reaction tube was then heated to 80° for 1·5 hour. No volatile products were obtained. The contents of the tube were poured into water to dissolve the precipitated sodium fluoride, and neutralised with sulphuric acid, and the lower layer removed. Distillation *in vacuo* gave a trace of unchanged 1-ethoxy-3 : 3 : 3-trifluoropropene and a residual liquid of higher b. p. Sulphuric acid (1 : 1) was added to the latter, and the mixture was heated to 40° at atmospheric pressure. The evolved gas was passed into 2 : 4-dinitrophenylhydrazine solution, and after 1 hour the temperature of the distilling flask was slowly raised to 120°. After the flask had been swept out with nitrogen, the precipitated 2 : 4-dinitrophenylhydrazone, recrystallised from ethanol, had m. p. 150—151°. The yield of βββ-trifluoropropaldehyde was 28%. Dilution of the sulphuric acid in the distilling flask gave no indication of the presence of residual organic material, and the material evolved by the sulphuric acid treatment reacted completely with the 2 : 4-dinitrophenylhydrazine solution. The sodium fluoride produced by reaction corresponded to *ca.* 50% of the ethoxytrifluoropropene taken.

Addition of Diethylamine to 3 : 3 : 3-Trifluoropropyne.—Trifluoropropyne (0·94 g.) was sealed with cuprous chloride (0·02 g.) and diethylamine (3 ml.), kept at room temperature for 4 hours, and slowly heated to 100°. Unchanged trifluoropropyne (0·11 g.) was recovered, and after pouring into water (fluoride present), distillation of the lower layer *in vacuo* gave 1-*diethylamino*-3 : 3 : 3-*trifluoropropene* (28%) (Found : N, 8·3%; *M*, 161. $C_7H_{12}NF_3$ requires N, 8·4%; *M*, 167), b. p. *ca.* 40°/105 mm. The still residue (0·4 g.) was qualitatively examined by infra-red spectroscopy in the 4 μ region and showed a band at 4·65 μ ascribable to a C≡C stretching frequency. Decomposition occurred on attempted distillation.

Addition of Hydrogen Halides to Hexafluorobut-2-yne.—(a) *Hydrogen chloride.* Hexafluorobutyne (0·81 g.) was sealed with a 20% excess of hydrogen chloride in a tube containing aluminium trichloride (0·1 g.). After being at room temperature for 3 hours, the tube was heated to 50° for 30 minutes, cooled, and opened. The non-gaseous products were transferred *in vacuo* to a distilling flask and fractionated to give 2-chloro-1 : 1 : 1 : 4 : 4 : 4-hexafluorobut-2-ene (65% yield) (Found : C, 24·0; H, 0·3%; *M*, 195. Calc. for C_4HClF_6 : C, 24·2; H, 0·5%; *M*, 198·5), b. p. 34—35°. Henne, Hinkamp, and Zimmerschied (*J. Amer. Chem. Soc.*, 1945, **67**, 1907) report b. p. 34·4° (see also Haszeldine, *J.*, 1952, 2504).

In another experiment with a 200% excess of hydrogen chloride, only the monochlorohexafluorobutene was isolated. Small amounts of material of higher b. p. were present in both experiments but could not be resolved into definite components on the scale used. Aluminium trifluoride was formed during reaction. Antimony pentachloride was also used to catalyse the addition of hydrogen chloride.

A further experiment on the same scale, with a 20% excess of hydrogen chloride in the absence of aluminium trichloride, gave a 78% yield of the chlorohexafluorobutene after 24 hours' heating at 100°.

Control experiments with hexafluorobut-2-yne and the 2-halogenohexafluorobut-2-enes showed that aluminium chloride or bromide did not bring about appreciable rearrangement under the conditions used.

(b) *Hydrogen bromide.* Hexafluorobut-2-yne (0·82 g.) and hydrogen bromide (20% excess) were sealed with aluminium bromide (0·1 g.) and left in the dark at 30° for 7 days. After removal of the excess of hydrogen bromide, distillation of the liquid products of reaction gave 2-bromo-1 : 1 : 1 : 4 : 4 : 4-hexafluorobut-2-ene (68%), b. p. 54—56°, and unidentified material of higher b. p. Aluminium fluoride was found to be present.

(c) *Hydrogen bromide under the influence of ultra-violet light.* There was no reaction between hexafluorobut-2-yne (0·81 g.) and hydrogen bromide (20% excess) after 24 hours in the dark at room temperature. Irradiation of the Pyrex tube with a Hanovia lamp brought about a rapid reaction, and after 2 hours the contents were distilled to give unchanged hexafluorobutyne (8%), hydrogen bromide, 2-bromo-1 : 1 : 1 : 4 : 4 : 4-hexafluorobut-2-ene (87%) (Found : C, 20·0; H, 0·3. Calc. for C_4HBrF_6 : C, 19·8; H, 0·4%), b. p. 55° (Haszeldine, *J.*, 1952, 2504, reports b. p. 55°), and a small amount (*ca.* 5%) of 2 : 3-dibromohexafluorobut-2-ene, b. p. 105—107° (Haszeldine, *loc. cit.*, reports b. p. 105°).

Addition of Methanol and Ethanol to Hexafluorobut-2-yne.—Methanol (15 ml.), in which

sodium (0·75 g.) had been dissolved, was sealed in a tube with hexafluorobutyne (1·51 g.), and set aside at 0° for 48 hours, then at 30° for 1 hour; 10% of the butyne was recovered unchanged, and after dilution by water, the reaction mixture was acidified with sulphuric acid, and the lower layer removed, washed, dried, and distilled to give 1 : 1 : 1 : 4 : 4 : 4-*hexafluoro*-2-*methoxybut*-2-*ene* (61% yield) (Found: C, 30·6; H, 1·8%; *M*, 195. $C_5H_4OF_6$ requires C, 30·9; H, 2·1%; *M*, 194), b. p. 55—57°, and a small amount of liquid with higher b. p. which was probably the ketal (see below). A qualitative test for fluoride ion was strongly positive.

Under similar conditions ethanol gave a 57% yield of 2-*ethoxy*-1 : 1 : 1 : 4 : 4 : 4-*hexafluorobut*-2-*ene* (Found: C, 34·4%; *M*, 205, 204. $C_6H_6OF_6$ requires C, 34·6%; *M*, 208), b. p. 72·5—73°; 8% of the hexafluorobutyne was recovered, and fluoride ion was again present. Oxidation with alkaline potassium permanganate yielded trifluoroacetic acid. The 2-methoxy- and 2-ethoxy-1 : 1 : 1 : 4 : 4 : 4-hexafluorobut-2-enes absorbed bromine quantitatively to give 2 : 3-*dibromo*-1 : 1 : 1 : 4 : 4 : 4-*hexafluoro*-2-*methoxybutane* (Found: C, 16·8. $C_5H_4Br_2F_6$ requires C, 16·9%), b. p. 58—59°/25 mm., n_D^{20} 1·408, and 2 : 3-*dibromo*-2-*ethoxy*-1 : 1 : 1 : 4 : 4 : 4-*hexafluorobutane* (Found: C, 19·9. $C_6H_6Br_2F_6$ requires C, 19·6%), b. p. 72—73°/32 mm., n_D^{20} 1·409, respectively. The 2-methoxy- and 2-ethoxy-1 : 1 : 1 : 4 : 4 : 4-hexafluorobutenes (1·0 g.) were heated in sealed tubes with constant-boiling hydriodic acid to give 51 and 55% yields of 1 : 1 : 1 : 4 : 4 : 4-hexafluorobutan-2-one, identified as described below.

Hydrogenation of 2-*Ethoxy*-1 : 1 : 1 : 4 : 4 : 4-*hexafluorobut*-2-*ene*.—Ethoxyhexafluorobutene (2·31 g.) was sealed in a small autoclave with hydrogen (10 atm.), Raney nickel (0·15 g.), and methanol (10 ml.), set aside for 0·5 hour, then heated to 120° for 0·5 hour. The pressure of hydrogen was maintained at 10 atm. throughout. The gaseous products were removed and found to contain ethane (88% of theory). The contents of the autoclave were added to water (20 ml.), and after filtration, addition of semicarbazide gave the semicarbazone of 1 : 1 : 1 : 4 : 4 : 4-hexafluorobutan-2-one (58% yield). The yield was estimated from the weight of semicarbazone, and is therefore probably lower than the true yield of ketone. The semicarbazone (Found: N, 17·8. Calc. for $C_5H_5N_3OF_6$: N, 17·7%), recrystallised from methanol, had m. p. 123°. Henne, Schmitz, and Finnegan (*loc. cit.*) report m. p. 122°. There was no indication of the formation of 2-ethoxy-1 : 1 : 1 : 4 : 4 : 4-hexafluorobutane.

Addition of Methanol and Ethanol to 2-*Alkoxy*-1 : 1 : 1 : 4 : 4 : 4-*hexafluorobut*-2-*enes*.—Ethoxyhexafluorobutene (1·65 g.) was sealed in a Carius tube with ethanol (10 ml.) containing sodium ethoxide (1 g.) and heated to 70° for 1 hour. After dilution with water and acidification with sulphuric acid, the lower layer was distilled to give 2 : 2-*diethoxy*-1 : 1 : 1 : 4 : 4 : 4-*hexafluorobutane* (59% yield) (Found: C, 38·0. $C_8H_{11}O_2F_6$ requires C, 38·0%), b. p. 135°, n_D^{20} 1·342. A qualitative test on the solution for fluoride was positive.

The diethoxyhexafluorobutane (0·51 g.) was heated under reflux with sulphuric acid (50%), and the volatile products condensed in semicarbazide solution to give the semicarbazone of 1 : 1 : 1 : 4 : 4 : 4-hexafluorobutan-2-one (53% yield), m. p. 122—123°.

In a similar manner, the interaction of 1 : 1 : 1 : 4 : 4 : 4-hexafluoro-2-methoxybut-2-ene (1·01 g.) and methanol in the presence of sodium methoxide gave 1 : 1 : 1 : 4 : 4 : 4-*hexafluoro*-2 : 2-*dimethoxybutane* (53%) (Found: C, 31·8. $C_6H_8O_2F_6$ requires C, 31·9%), b. p. 50°/100 mm. Hydrolysis of this compound by the method described above gave 1 : 1 : 1 : 4 : 4 : 4-hexafluorobutan-2-one in 48% yield. In both cases the hydrolysis was accompanied by appreciable decomposition, and it is possible that the use of dilute acid would give better results.

Addition of Diethylamine to Hexafluorobut-2-*yne*.—Diethylamine (5 ml.) and hexafluorobutyne (1·42 g.) were sealed in a Carius tube which, after 4 days, was heated to 50° for 5 hours. Treatment with excess of water caused separation into two layers, and after being washed and dried the lower layer was distilled to give 2-*diethylamino*-1 : 1 : 1 : 4 : 4 : 4-*hexafluorobut*-2-*ene* (57% yield) (Found: N, 6·0. $C_8H_{11}NF_6$ requires N, 6·0%), b. p. 72—74°/150 mm., 123°/760 mm. (micro), n_D^{20} 1·371.

Analysis for Carbon and Hydrogen.—These were determined by pyrolysis of the fluorine compound in a silica tube packed with silver vanadate and heated to 800°.

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670. *The Synthesis of γ-Resorcylic Acid (2 : 6-Dihydroxybenzoic Acid).*

By N. J. Cartwright, J. Idris Jones, and Diana Marmion.

With the object of providing a suitable quantity of sodium γ-resorcylate for clinical tests in cases of rheumatic fever (Reid, Watson, Cochran, and Sproull, *Brit. Med. J.*, 1951, 321), known methods of preparing γ-resorcylic acid have been re-investigated and a new synthesis evolved. Mauthner's synthesis from *m*-dinitrobenzene leads to an overall yield of 12%. A convenient synthesis from 2 : 6-dihydroxyacetophenone is described, involving methylation, hypochlorite oxidation, and demethylation with aluminium chloride. Parham and Anderson's method is suitable for small-scale operation and adaptable for the preparation of γ-resorcylic acid isotopically labelled in the carboxyl group. The ultra-violet absorption spectra of γ-resorcylic acid and some related compounds are recorded.

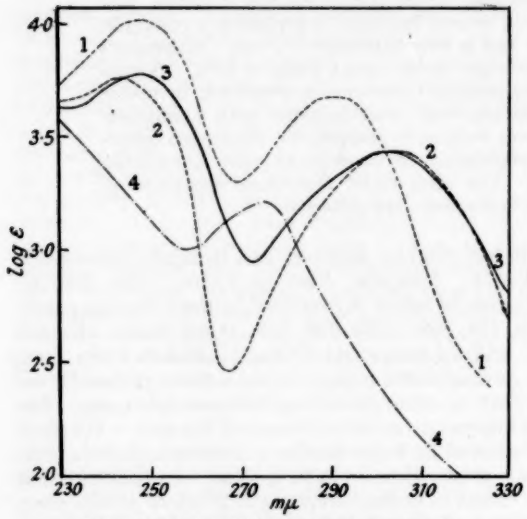
γ-Resorcylic acid was first prepared in low yield by Senhofer and Brunner (*Sitzungsber. Akad. Wiss. Wien*, 1879, **80**, II, 504, 514; *Jahresber. Fortschr. Chem.*, 1880, 835) by carboxylation of resorcinol, a re-investigation of which is described in the following paper. Mauthner's synthesis (*J. pr. Chem.*, 1929, **121**, 259; 1930, **124**, 319), in our hands, afforded at best only a 12% yield of γ-resorcylic acid. Limaye and Kelkar (*J. Indian Chem. Soc.*, 1935, **12**, 788; *Rasayanam*, 1936, **1**, 24) have reported a synthesis of γ-resorcylic acid from 3-acetyl-5-hydroxy-2-methylchromone derived from 2 : 6-dihydroxyacetophenone. The last compound affords a convenient starting point for the synthesis of the acid. We have found that methylation of the ketone followed by hypochlorite oxidation and demethylation with aluminium chloride furnishes γ-resorcylic acid in 91% yield. In the oxidation stage, failure to remove completely the excess of sodium hypochlorite before acidification results in the formation of some 3-chloro-2 : 6-dimethoxybenzoic acid. The orientation of this chloro-derivative was established by demethylation and then decarboxylation to 4-chlororesorcinol. 2-Hydroxy-6-methoxyacetophenone, obtained as a by-product of the methylation of 2 : 6-dihydroxyacetophenone, was converted by Limaye and Kelkar's method (*loc. cit.*, 1936) into 2-hydroxy-6-methoxybenzoic acid for comparison of its ultra-violet absorption spectrum with that of γ-resorcylic acid.

2-Methylresorcinol exists in the aqueous liquors from the low-temperature carbonisation of coal and is commercially available (Baker, Bondy, McOmie, and Tunnicliff, *J.*, 1949, 2835). Alkaline permanganate oxidation of its dimethyl ether furnished 2 : 6-dimethoxybenzoic acid and thence γ-resorcylic acid. An elegant synthesis of the γ-acid by Parham and Anderson (*J. Amer. Chem. Soc.*, 1948, **70**, 4187) involves metalation, with *n*-butyl-lithium, of the acetal formed from resorcinol and dihydropyran, followed by carboxylation and acid hydrolysis. This method is eminently suitable for small-scale preparations and offers a satisfactory route to the acid isotopically labelled in the carboxyl group. With this in mind, the synthesis was carried through on a *ca.* 5-millimole scale under conditions that would obtain in an isotopic synthesis and gave a 51% yield.

The ultra-violet absorption spectra of 2 : 6-dihydroxy-, 2-hydroxy-6-methoxy-, 2 : 6-dimethoxy-, and 2 : 4-dihydroxy-benzoic acid in water in the region 2300—3300 Å are recorded in Fig. 1. Since this work was done, Moser and Kohlenberg (*J.*, 1951, 804) have recorded and discussed the ultra-violet absorption spectra of a series of substituted benzoic acids, including 2 : 6-dihydroxy- and 2 : 6-dimethoxy-benzoic acid, in 95% ethyl alcohol. Our data for 2 : 6-dimethoxybenzoic acid in water are essentially the same as those given by these authors. However, for γ-resorcylic acid the spectra are significantly different in the range 2650—3000 Å. Moser and Kohlenberg record a weakly-defined peak near 2770 Å (log ε 3·29), of which we find no evidence. We believe that their sample of γ-resorcylic acid, prepared by Limaye and Kelkar's method (*loc. cit.*), was probably impure, resorcinol being the likely impurity (this could arise from decarboxylation during the hydrolysis or during purification by crystallisation). At ~2770 Å, where Moser and Kohlenberg observed

the ill-defined maximum, resorcinol has a strong absorption band ($\lambda_{max.}$ 2760, log ε 3·30) (Morton and Stubbs, *J.*, 1940, 1347; Hodgson, *J.*, 1943, 380; Adams, Cain, and Wolff, *J. Amer. Chem. Soc.*, 1940, **62**, 732). The absence of marked absorption by resorcinol in the region of the two maxima for γ-resorcylic acid accounts for the close correspondence found for the values of log ε at these wave-lengths.

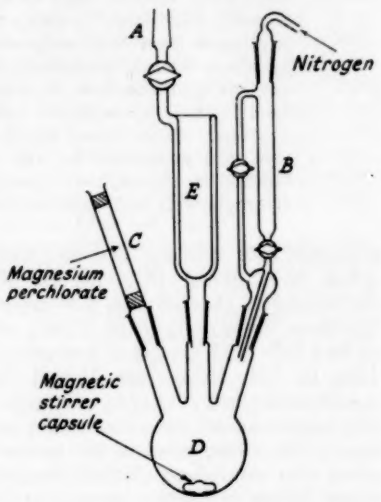
FIG. 1.



Ultra-violet absorption spectra, in water, of:

1, 2 : 4-*Dihydroxybenzoic acid*; 2, 2 : 6-*dihydroxybenzoic acid*; 3, 2-*hydroxy*-6-*methoxybenzoic acid*; 4, 2 : 6-*dimethoxybenzoic acid*.

FIG. 2.



EXPERIMENTAL

Microanalyses are by Miss M. Corner.

Mauthner's Synthesis.—For the preparation of 2 : 6-dimethoxybenzonitrile Russell and Tebbens's procedure (*Org. Synth.*, **22**, 35) was slightly modified. Potassium cyanide (690 g.) in water (1200 c.c.) was added to technical-grade *m*-dinitrobenzene (1500 g.) in methyl alcohol (22·5 l.). The mixture was stirred at 40° for 2 hours, and then set aside for at least 2 days. Cold water (200 l.) was added and the precipitate allowed to resettle overnight, filtered off, pressed, dried in air 2—3 days, and extracted exhaustively with chloroform (Soxhlet). The extract was concentrated to 1500 c.c. by distillation and light petroleum (3 l.; b. p. 60—80°) was added. The precipitated red 6-methoxy-2-nitrobenzonitrile was collected and air-dried (yield from 3 runs, 1390 g., 25%).

The crude nitrile (250 g.) with potassium hydroxide (160 g.) in methyl alcohol (3·8 l.) gave 2 : 6-dimethoxybenzonitrile (17·6%, based on the *m*-dinitrobenzene). This (100 g.) was hydrolysed for 48 hours with potassium hydroxide (2500 g.) in boiling water (5 l.). On cooling, potassium 2 : 6-dimethoxybenzoate crystallised and was removed by filtration and dissolved in the minimum amount of water, and the solution acidified with concentrated hydrochloric acid. The crude acid was filtered off and dried and, since it was advantageous to purify it before demethylation, was extracted (Soxhlet) with benzene. The average yield of purified 2 : 6-dimethoxybenzoic acid, m. p. 186—187°, was 14·8% based on *m*-dinitrobenzene.

For demethylation (cf. Mauthner, *loc. cit.*) free-flowing, sublimed, anhydrous aluminium chloride (Grant and Hardy, B.P. Appl. 19,247/49) was advantageous. The following experiment was typical. To 2 : 6-dimethoxybenzoic acid (125 g.) in benzene (3·5 l.), aluminium chloride (400 g.) was added, and the mixture heated for 2 hours under reflux, with constant stirring. The solution was cooled, poured on ice (2 kg., not more) and later filtered. The aqueous layer was made strongly acid with concentrated hydrochloric acid. γ-Resorcylic acid

separated as needles; a further small quantity was obtained by washing the filtered benzene-insoluble solids with sodium carbonate solution and acidification. In this way, γ-resorcylic acid, m.p. 160—163° (decomp.) after crystallisation from benzene, was obtained in 95—98% yield. Although the acid may be crystallised safely from benzene, some decarboxylation occurs in boiling toluene and, to a smaller extent, in boiling water. Use of the above grade of aluminium chloride led to less amorphous material which, in appreciable quantity, leads to thick emulsions from which separation of the aqueous phase containing the γ-resorcylic acid is difficult.

Synthesis of γ-Resorcylic Acid from 2 : 6-Dihydroxyacetophenone.—2 : 6-Dihydroxyacetophenone (Russell and Frye, *Org. Synth.*, **21**, 22; finally crystallised from toluene) and free-flowing sublimed anhydrous aluminium chloride (cf. above) gave 7-acetoxy-4-methylcoumarin in 76—79% yield. The precautions given by Russell and Frye (*loc. cit.*) for decomposing the aluminium chloride complex appear to be unnecessary and in general water was added and the decomposition allowed to take place rapidly, with external cooling if necessary. In addition, completion of the decomposition was effected by adding dilute hydrochloric acid in one stage instead of gradually.

Two routes were investigated for the methylation of 2 : 6-dihydroxyacetophenone.

(*a*) To the ketone (133 g.), suspended in water (100 c.c.) under nitrogen, sodium hydroxide (140 g.) in water (150 c.c.) was added and then methyl sulphate (320 g.) at a rate sufficient to maintain gentle ebullition, and the mixture was then heated on a steam-bath for 30 minutes. A further quantity of methyl sulphate (50 g.) was added, followed by 2N-sodium hydroxide to alkalinity. The mixture was cooled and the product filtered off and washed with water. Pure 2 : 6-dimethoxyacetophenone (127 g.), b.p. 118—120°/1·5 mm., m. p. 65—66°, was obtained by distillation of the product.

(*b*) 2 : 6-Dihydroxyacetophenone (100 g.), anhydrous potassium carbonate (220 g.), and methyl iodide (200 g.) in acetone (600 c.c.) were heated under reflux for 12 hours. After filtration and washing with acetone, the combined filtrates were evaporated and the oily residue was taken up in ether and washed with N-sodium hydroxide. The ethereal solution was dried and the residue after removal of the solvent was purified by crystallisation from light petroleum (b.p. 60—80°), giving pure 2 : 6-dimethoxyacetophenone (95 g.). Distillation is preferred for purification, affording a cleaner product in higher yield (93—97%).

It was advisable to use purified dimethoxy-ketone for the oxidation. Sodium hydroxide (110 g.) in water (100 c.c.) was added to ice (1 kg.) and chlorine passed through until the solution was neutral to litmus (or 89 g. of chlorine). Further sodium hydroxide (50 g.) in water (200 c.c.) was then added. To the resulting solution at 65°, the ketone (60 g.) was added portion-wise during ½ hour : the temperature rose to 85° and was kept thereat for a further 1½ hours. After cooling, excess of sodium hydrogen sulphite (100 g.) was added to destroy unchanged hypochlorite, and the solution was acidified (Congo-red) with hydrochloric acid. When cold the precipitated acid was washed with cold water, then benzene, and dried, giving 2 : 6-dimethoxybenzoic acid, m. p. 185—187° (58 g., 97%), pure enough for demethylation (see above).

For the preparation of the sodium salt, γ-resorcylic acid (100 g.) was washed with saturated sodium chloride solution to remove traces of aluminium salts and then dissolved in N-sodium hydrogen carbonate (300 c.c.) at 70°. Solid sodium hydrogen carbonate (~25—30 g.) was then added gradually until no further reaction ensued. The solution was filtered hot and cooled to 0°. The sodium salt was filtered off and recrystallised from 0·5N-sodium hydrogen carbonate (minimum volume) at 70—80° and the whole cooled to 0°. If necessary, the salt was finally washed with saturated sodium chloride solution to remove colour.

2-Hydroxy-6-methoxybenzoic Acid.—2-Hydroxy-6-methoxyacetophenone, m. p. 58°, was obtained as a by-product from the methylation of 2 : 6-dihydroxyacetophenone by washing the methylated product with sodium hydroxide solution and acidification. It was also prepared in 60% yield by methylating 2 : 6-dihydroxyacetophenone with one equivalent of methyl iodide, as described by Nakazawa (*J. Pharm. Soc. Japan*, 1939, **59**, 495). It was converted by Limaye and Kelkar's procedure (*loc. cit.*) into 2-hydroxy-6-methoxybenzoic acid, m. p. 134° (Found : C, 57·3; H, 4·9. Calc. for $C_8H_8O_4$: C, 57·1; H, 4·8%), in low yield.

3-Chloro-2 : 6-dimethoxybenzoic Acid.—In the above oxidation of 2 : 6-dimethoxyacetophenone incomplete removal of the excess of hypochlorite before acidification results in the formation of some *3-chloro-2 : 6-dimethoxybenzoic acid*, shining plates (from benzene), m. p. 132° (Found : C, 49·8; H, 4·3. $C_9H_9O_4Cl$ requires C, 49·8; H, 4·2%).

The acid (2 g.) was heated for 4 hours with aluminium chloride (6 g.) in benzene (100 c.c.). After cooling, the mixture was poured on ice (40 g.) and set aside. The aqueous layer was acidified with concentrated hydrochloric acid and extracted with ether. Treatment of the

ethereal extract with bicarbonate solution and acidification thereof furnished 3-*chloro*-2 : 6-*dihydroxybenzoic acid* (1·65 g.), m. p. 193° after two crystallisations from benzene (Found : C, 44·7, H, 2·8; Cl, 18·3. $C_7H_5O_4Cl$ requires C, 44·5; H, 2·7; Cl, 18·8%). With ferric chloride solution the acid gave a blue colour. On distillation the acid (1 g.) boiled with decarboxylation at about 260° and was converted into 4-chlororesorcinol (0·65 g.), m. p. 89° undepressed on admixture with an authentic specimen.

Oxidation of 2-*Methylresorcinol.*—To 2-methylresorcinol (50 g.) in a solution of sodium hydroxide (65 g.) in water (250 c.c.) was added methyl sulphate (100 g.) during 15 minutes. The mixture was then heated for 2 hours on a steam-bath, cooled, and extracted with ether. The dried ethereal extract, on removal of the solvent and crystallisation of the residue from benzene, furnished 2 : 6-dimethoxytoluene (57 g.).

2 : 6-Dimethoxytoluene (10 g.) in water (200 c.c.) was treated with potassium permanganate (20·7 g.) during 1 hour at 80°. After being kept overnight the precipitate was filtered off and washed. Acidification of the filtrate furnished 2 : 6-dimethoxybenzoic acid (8·74 g., 73%), m. p. 189°, and ether-extraction of the precipitate afforded unchanged 2 : 6-dimethoxytoluene (1·4 g.).

Parham and Anderson's Synthesis.—Resorcinol bistetrahydro-2-pyranyl ether, prepared as described by Parham and Anderson (*loc. cit.*) and fractionally distilled, was a colourless syrup, b. p. 199°/~2 mm., which crystallised.

n-Butyl-lithium was prepared by Reid's method (quoted in Calvin, Heidelberger, Reid, Tolbert, and Yankwich, "Isotopic Carbon," Chapman and Hall, London, 1949, p. 184), the resulting pentane solution being analysed by Gilman and Haubein's method (*J. Amer. Chem. Soc.*, 1944, **66**, 1515).

A pentane solution (12 ml.) of *n*-butyl-lithium (6 millimoles) was run into flask *D* (Fig. 2) in a current of dry nitrogen from the calibrated dropping-funnel *B*. The flask was connected at *A*, through the condenser *E*, to the vacuum-manifold described by Cox, Turner, and Warne (*J.*, 1950, 3167). Drying-tube *C* was replaced by a stopper, and pentane was distilled from the flask at *ca.* 0·5 atm. until only 1 ml. remained. Pure ether (15 ml.; stored over sodium) was then distilled into *D*, and the stirrer-capsule was agitated. Dry resorcinol bistetrahydro-2-pyranyl ether (1·58 g., 5·7 millimoles) in dry ether (10 ml.) was added quickly through the dropping-funnel. The mixture was warmed under reflux, with solid carbon dioxide in the condenser, for 6 hours and then set aside at room temperature for 16 hours. After the flask had been cooled in liquid nitrogen and evacuated, the contents were warmed to −60° and subjected to vigorous magnetic stirring. Carbon dioxide (15·25 millimoles) was then admitted to the lithium solution; absorption was rapid, the pressure falling from 60 to 10 cm. after 30 seconds and to 8 cm. after a further 2½ minutes. Nitrogen was admitted and the lithium complex decomposed by 15% hydrochloric acid (15 ml.). 2·45 Millimoles of carbon dioxide remained in the vacuum system, *i.e.*, 12·8 millimoles had been absorbed. The reaction mixture was stirred until all solid had dissolved, then the two layers were separated. The aqueous layer was extracted with six portions of ether; the combined extracts were treated with saturated sodium hydrogen carbonate solution (15 ml.), and the aqueous phase separated and acidified. The acid solution was exhaustively extracted with ether. Evaporation of the ether left a residue which on crystallisation from benzene afforded 2 : 6-dihydroxybenzoic acid (0·45 g., 51%), m. p. 168° (microscope and block).

Ultra-violet Absorption Spectra.—The spectra of β- and γ-resorcylic and 2 : 6-dimethoxy- and 2-hydroxy-6-methoxy-benzoic acid in water were measured with a Unicam Model S.P. 500 Quartz Spectrophotometer.

This work, which was undertaken at the request of the Medical Research Council, formed part of the programme of the Chemistry Research Board and is published by permission of the Director of the Chemical Research Laboratory. The authors acknowledge the valuable assistance of Mr. Sidney Hunt and Mr. A. H. G. Pettit with the preparative work and of Mr. W. Kynaston with the spectra determinations. Thanks are also offered to Dr. J. D. Cox for evaluating the Parham and Anderson synthesis.

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671. *The Carboxylation of Resorcinol and the Separation of β- and γ-Resorcylic Acid by Ion-exchange Chromatography.*

By D. K. Hale, Audrey R. Hawdon, J. Idris Jones, and D. I. Packham.

Yields of γ-resorcylic acid afforded by various modifications of the Kolbe–Schmitt reaction have been explored and methods of separating the acid from the accompanying β-isomer have been studied. Selective elution of the acids from a column of an anion-exchange resin in the chloride form with solutions of hydrochloric acid in water or aqueous alcohol effects complete separation. A process for the partial conversion of β- into γ-resorcylic acid is reported.

Salient information on the Kolbe–Schmitt reaction (Kolbe, *Annalen*, 1859, **113**, 126; 1860, **115**, 157; Schmitt, *J. pr. Chem.*, 1885, **31**, 397) for the carboxylation of phenols has been summarised by Cameron, Jeskey, and Baine (*J. Org. Chem.*, 1950, **15**, 233), and Wessely, Benedikt, Benger, Friedrich, and Prillinger (*Monatsh.*, 1950, **81**, 1071). Conflicting claims have been made for the preparation of β- and γ-resorcylic acid by this reaction (Senhofer and Brunner, *Sitzungsber. Akad. Wiss. Wien*, 1879, **80**, II, 504, 514; *Jahresber. Fortschr. Chem.*, 1880, 835; Bistrzycki and von Kostanecki, *Ber.*, 1885, **18**, 1985; Brunner, *Annalen*, 1907, **351**, 320; *Monatsh.*, 1928, **50**, 216; Mauthner, *J. pr. Chem.*, 1930, **124**, 322; von Hemmelmayr, *Monatsh.*, **1917**, **38**, 81; Clibbens and Nierenstein, *Org. Synth.*, **10**, 94). The nature of the alkali salt is known to influence both the course and extent of the reaction (Ferguson, Holmes, and Calvin, *J. Amer. Chem. Soc.*, 1950, **72**, 5315; Cameron *et al.*; Wessely *et al.*, *locc. cit.*; Morgan, *J. Soc. Chem. Ind.*, 1931, **50**, 104) but it is not clear from earlier work whether this is so for resorcinol.

Cartwright, Jones, and Marmion (preceding paper) studied various preparative methods for γ-resorcylic acid and investigation of the direct carboxylation of resorcinol is reported in the present paper.

Heating resorcinol with excess of potassium or sodium hydrogen carbonate in water for a short period afforded exclusively β-resorcylic acid, the potassium salt giving the higher yield. Passage of a rapid stream of carbon dioxide through the mixture did not greatly influence the result. Prolonging the treatment with potassium hydrogen carbonate and carbon dioxide gave some γ-resorcylic acid: *e.g.*, after 41 hours 50% and 36% of β- and γ-acid respectively were obtained. Use of a higher temperature, by substitution of glycerol for water as the reaction medium, with potassium hydrogen carbonate did not materially influence either the course or extent of the reaction. On the other hand, increasing the pressure of carbon dioxide to 27 atms. speeded the reaction and afforded quantitative carboxylation at 120—130°, 48% of the product being γ-resorcylic acid. Much the same results were obtained whether the mono- or the di-potassium derivative of resorcinol was used. The lithium derivatives gave less carboxylation, both β- and γ-acid being formed; ammonium hydrogen carbonate yielded exclusively β-acid. Carboxylation of the anhydrous disodium or dipotassium salt of resorcinol in benzene gave virtually quantitative yields of acid, but only with the dipotassium salt could γ-resorcylic acid be detected, and then only a trace. Carboxylation of resorcinol at 175° with potassium carbonate and carbon dioxide (60 atms.) according to Marassé's technique (G.P. 76,441/1894) led to 90% conversion, γ-acid comprising about 15% of the product. Sodium carbonate, in like manner, furnished only 35% of acids, only 4% of which was the γ-isomer. An attempt to carboxylate resorcinol in pyridine at 160—170° with carbon dioxide (50 atms.) was unsuccessful.

It appears from some of the experiments that the first product is the β-acid, γ-resorcylic acid being subsequently formed by rearrangement. *E.g.*, when the mono-sodium or -potassium salt of β-resorcylic acid was heated in water at 200° part of the acid (26·6% and 19·5% respectively) was recovered as the γ-isomer. Resorcinol was also formed and carbon dioxide liberated. This rearrangement of β- to γ-resorcylic acid through its alkali metal salt is analogous to the formation of dipotassium *p*-hydroxybenzoate, phenol, and carbon dioxide from potassium salicylate (Ost, *J. pr. Chem.*, 1875, [ii], **11**, 24, 385). Unlike sodium salicylate, sodium γ-resorcylate also undergoes rearrangement.

β- and γ-Resorcylic acid may be separated, although somewhat tediously, by fractional crystallisation at ≯80°. Above 80° γ-resorcylic acid tends to be decarboxylated. Baker (*Nature*, 1936, **137**, 236) has drawn attention to the high acid strength of γ-resorcylic acid compared with the β-acid (K $5{\cdot}0 \times 10^{-2}$ and $0{\cdot}52 \times 10^{-3}$ respectively; cf. Abichandani and Jatkar, *J. Indian Inst. Sci.*, 1941, **23**, *A*, 77), which he attributes to the double chelation of the γ-acid anion. It was therefore considered that ion-exchange chromatography should provide convenient separation.

Ion-exchange chromatography has been used extensively for separation of complex mixtures of amphoteric electrolytes such as amino-acids (Partridge, *Chem. and Ind.*, 1950, 383; Moore and Stein, *J. Biol. Chem.*, 1951, **192**, 663) and mononucleotides (Cohn, *J. Amer. Chem. Soc.*, 1950, **72**, 1471), but its use for relatively simple carboxylic acids has received little attention. For the separation of weak electrolytes which differ appreciably in their dissociation constants it is usually convenient to base the separation on differences in the solution equilibria rather than on differences in the affinities of the ions for the ion-exchange resin. Thus Davies (*Biochem. J.*, 1949, **45**, 38) has shown that, for the separation of two weak acids by elution, the best separation will normally be achieved when the pH of the solution applied to the resin is 1—2 units lower than the value of $\frac{1}{2}(pK + pK')$ where K and K' are the dissociation constants of the two acids. The weaker acid will then be less readily taken up by the resin and will be preferentially eluted.

When aqueous eluting agents were employed for the separation of β- and γ-resorcylic acid, large volumes of eluants were required owing to the "tailing" of the bands. This effect which has been frequently observed in the chromatographic separation of organic acids was however overcome by the addition of alcohol to the eluting agent (cf. Moore and Stein, *loc. cit.*, who added butyl alcohol to the eluting agent employed for the removal of the aromatic amino-acids). Separation of the resorcylic acids was most readily achieved by absorbing the mixture on an anion-exchange resin in the chloride form and then selectively eluting the β- and the γ-acid with 0·01N- and 0·1N-hydrochloric acid respectively in 75% ethyl alcohol.

Substitution in 7-hydroxy-4-methylcoumarin, derived from resorcinol by condensation with acetoacetic ester, generally yields 8-substituted derivatives as the initial and principal products. It seemed of interest to see whether the 8-carboxylic acid could be obtained exclusively by carboxylation and whether this would yield γ-resorcylic acid on hydrolysis with strong alkali. Carboxylation of the potassium salt of the coumarin at 180° yielded 47% of 7-hydroxy-4-methylcoumarin-8- plus -6-carboxylic acid. A small amount of resorcinol-2 : 4-dicarboxylic acid was also formed in one experiment, presumably by hydrolysis followed by carboxylation. The 6-acid has been prepared by Shah, Sethna, Banerjee, and Chakravarti (*J. Indian Chem. Soc.*, 1937, **14**, 717) by condensing β-resorcylic acid with acetoacetic ester in presence of sulphuric acid. An authentic sample of the 8-acid was prepared by us in the same way from γ-resorcylic acid. On hydrolysis with 20% sodium hydroxide solution it afforded some γ-resorcylic acid but considerable decarboxylation occurred simultaneously, yielding resorcinol.

Experimental

Microanalyses are by Miss M. Corner.

Carboxylation of Resorcinol.—Resorcinol (40 g.) and sodium hydrogen carbonate (200 g.) in water (400 c.c.) were heated on a steam-bath for 1½ hours and finally boiled. After cooling, the mixture was acidified with hydrochloric acid and extracted with ether. The resorcylic acid was removed from the ethereal extract by aqueous sodium hydrogen carbonate and recovered by acidification and extraction with ether. The crude solid remaining after removal of the solvent, crystallised from water (≯80°), gave pure β-resorcylic acid (23·5 g.), m. p. 213° (decomp.). With alcoholic ferric chloride solution the acid gave a red colour. No trace of γ-resorcylic acid could be detected. Resorcinol (19·5 g.) was recovered from the original ethereal extract.

Resorcinol (236 g.) and potassium hydrogen carbonate (1500 g.) in water (2 l.), when heated under the same conditions, afforded 302 g. of β-resorcylic acid, and 15 g. of resorcinol were recovered unchanged. Again, no γ-resorcylic acid was detected.

When the directions of Clibbens and Nierenstein (*loc. cit.*) were followed and the mixture was

heated on the steam-bath for 4 hours and then under reflux for ½ hour, with a rapid stream of carbon dioxide passing through the solution, potassium hydrogen carbonate gave a 57% yield of pure β-acid, 30% of resorcinol being recovered. Similarly, sodium hydrogen carbonate gave a 50% yield of β-acid with 27% recovery of resorcinol. In both experiments substitution occurred exclusively in the β-position.

Resorcinol (75 g.) and potassium hydrogen carbonate (110 g.), dissolved in the minimum amount of water at room temperature, were heated under reflux (~110°) for 16 hours with a rapid stream of carbon dioxide passing through the solution. After cooling, the solution was acidified with hydrochloric acid. The precipitated solids were filtered off and washed with cold water, and on crystallisation from hot water gave pure β-resorcylic acid (15·8 g.). The filtrate was exhaustively extracted with ether and the extract treated with sodium hydrogen carbonate solution, which on acidification and further ether-extraction afforded a further quantity of β-acid (8 g. after crystallisation). The filtrate was extracted with ether, the ether removed, and the solid crystallised from boiling benzene and recrystallised from aqueous sodium chloride at >80°. In this way, pure γ-resorcylic acid (18·5 g.), m. p. 163—165° (decomp.), was obtained. With alcoholic ferric chloride solution γ-resorcylic acid gives an intense blue colour. From the original ethereal extract resorcinol (30 g.) was recovered. This method of separating β- and γ-resorcylic acid was generally followed in subsequent experiments.

Acids were obtained in 86% yield by heating resorcinol (110 g.), potassium hydrogen carbonate (500 g.), and water (700 g.) under reflux (~110°) for 41 hours with passage of a stream of carbon dioxide, giving β- (77·5 g.) and γ-resorcylic acid (56 g.).

Resorcinol (110 g.) and potassium hydrogen carbonate (200 g.) in glycerol (300 g.) at 130—140° (22 hours) with admission of a stream of carbon dioxide gave β- (47 g.) and γ-resorcylic acid (23·7 g.).

The following results illustrate the effect, principally, of pressure :

Reactants			Conditions			Products		
Resorcinol (g.)	Alkali (g.)	Water (g.)	Temp.	Max. CO_2 press. (atms.)	Time (hr.)	Resorcinol (g.)	β-Acid (g.)	γ-Acid (g)
55	200 $KHCO_3$	300	130°	27	3·5	—	39	36
110	400 ,,	500	93	34	4	35	55·5	44·5
110	140 ,,	100	120	17	5	—	142	10 *
110	100 ,,	100	119	18	6·25	5	80	60
156	160 KOH	400	109	13·5	4	52	103	20
110	56 ,,	200	108	13·5	3	20	66	26

* The reactants were not brought into solution by warming before insertion in the autoclave, as with the other mixtures. This may account for the seemingly anomalous result.

Lithium carbonate (18·5 g.) and resorcinol (27·5 g.) in water (300 c.c.) were heated under reflux for 8 hours with passage of carbon dioxide. The bulk of the resorcinol (24 g.) was recovered unchanged and the acid product (3 g.) consisted entirely of β-acid. No acid was formed by treatment of resorcinol (23 g.) with lithium carbonate (15 g.) in glycerol (200 c.c.) at 160—180° for 24 hours (carbon dioxide stream). Failure to effect any appreciable reaction with lithium carbonate may be due to the low solubility of the carbonate. Resorcinol (132 g.) in water (200 c.c.) containing lithium hydroxide (60 g.) at 110° (6 hours) with carbon dioxide (40 atms.) furnished 45 g. of acid, 88 g. of resorcinol being recovered. Fractional crystallisation yielded 33 g. of β- and 8 g. of γ-resorcylic acid. Ammonium hydrogen carbonate (150 g.) and resorcinol (110 g.) in water (400 c.c.) (carbon dioxide, 50 atms.) at 110—125° (6 hours) furnished only β-resorcylic acid (83 g.).

The disodium salt of resorcinol (21·5 g.) was suspended in benzene and the last traces of water were removed by azeotropic distillation. This suspension in benzene (~200 c.c.) was transferred to an autoclave and heated with carbon dioxide (40 atms.) at 110—130° for 3 hours, and then for 3 hours at 130—140°. A nearly quantitative recovery of β-resorcylic acid (30 g.) was obtained. Resorcinol (43 g.), as its dipotassium salt, when similarly treated also gave a theoretical yield of carboxylic acid (60 g.) but in this case a small amount (1 g.) of γ-resorcylic acid was present.

An attempt to carboxylate resorcinol (110 g.) in pyridine (300 g.) solution by heating it with carbon dioxide (40 atms.) at 160—170° for 6 hours proved unsuccessful, resorcinol (109·4 g.) being recovered unchanged.

In accordance with Marassé's technique (*loc. cit.*) resorcinol (55 g.) was heated with anhydrous potassium carbonate (250 g.) and carbon dioxide (25 atms.). The temperature was raised

slowly from 120° to 175° during 3 hours, the pressure attaining 60 atms. at the final temperature. This results in 89·5% of carboxylation, the product comprising β- (53 g.) and γ-resorcylic acid (10·5 g.). A slightly higher temperature (4½ hours at 150—190°, maximum pressure of carbon dioxide 65 atms.) furnished a 91·5% yield of acid product—56 g. of β- and 9 g. of γ-acid. Anhydrous sodium carbonate (300 g.) and resorcinol (55 g.) when similarly treated (5 hours at 150—184°, 43 atms. carbon dioxide) gave only 35% of acids (β, 24 g.; and γ, 1 g.).

Rearrangement of β- *to* γ-*Resorcylic Acid.*—When an aqueous solution of sodium β-resorcylate (from 77 g. of β-acid and 42 g. of sodium hydrogen carbonate) was heated at 200° for 5 hours the product consisted of a mixture of β- (21 g.) and γ-resorcylic acid (20·5 g.) and resorcinol (13 g.). Carbon dioxide was also generated during the reaction; a pressure of 3 atms. was registered after cooling to room temperature. Similarly, the potassium salt (from 77 g. of β-acid and 50 g. of potassium hydrogen carbonate), dissolved in the minimum quantity of water, when heated for the same period at the same temperature yielded on acidification β-acid (19·5 g.), γ-acid (15 g.), and resorcinol (16·5 g.). Free carbon dioxide liberated during the reaction led to a residual pressure of 4 atms. Repetition of the latter experiment at 166° led to a partial conversion of β-resorcylic acid (38 g.) into γ-acid (11 g.), resorcinol (14·2 g.), and carbon dioxide; part of the starting material (6·5 g.) was recovered unchanged. The presence of carbon dioxide and potassium hydrogen carbonate did not inhibit the reaction. Thus, when a solution of potassium β-resorcylate and potassium hydrogen carbonate (β-acid 80 g., potassium hydrogen carbonate 100 g., water 400 g.) was heated at 160° for 5 hours with an initial pressure of carbon dioxide of 7 atms. the product on acidification consisted of unchanged β-acid (34 g.), γ-acid (26 g.), and resorcinol (15 g.). Experiments in aqueous glycerol at 130° indicated that the reaction also takes place to some extent at this temperature.

Carboxylation of 7-*Hydroxy*-4-*methylcoumarin.*—Potassium hydrogen carbonate (150 g.), 7-hydroxy-4-methylcoumarin (76 g.), and water (300 g.) were heated for 5 hours at 110° with carbon dioxide (40 atms.). The coumarin was recovered unchanged. The same reactants, when heated for 3 hours at 150° with carbon dioxide (50 atms.), gave mixed acids (28·8 g.). After 3 hours at 180° with carbon dioxide (34 atms.) 7-hydroxy-4-methylcoumarin (50 g.) potassium hydrogen carbonate (150 g.), and water (300 g.) furnished a 47% yield of acidic material. The reaction products were treated as follows. After acidification and exhaustive ether-extraction the acids were removed with bicarbonate solution. Acidification of the bicarbonate extract yielded a solid which was filtered off and washed with water. Ether-extraction of the filtrate afforded a little more acid. Crystallisation of the crude acid from aqueous sodium chloride yielded an insoluble residue and colourless crystals, m. p. 201—202° (decomp.) after crystallisation from aqueous alcohol. This was 7-*hydroxy*-4-*methylcoumarin*-8-*carboxylic acid* (Found: C, 60·2; H, 3·7. $C_{11}H_8O_5$ requires C, 60·0; H, 3·6%). Extraction with ethyl acetate provided better separation, the 8-carboxylic acid being readily soluble therein. The insoluble residue, m. p. 278—282° (decomp.) on crystallisation from aqueous alcohol, gave 7-hydroxy-4-methylcoumarin-6-carboxylic acid, m. p. 282—284° (decomp.) [lit., 284—285° (decomp.)] (Found: C, 60·3; H, 3·8%). An authentic sample, m. p. 282—284° undepressed on admixture with the above, was prepared by the method of Shah *et al.* (*loc. cit.*). The 8-carboxylic acid (5·6 g.), m. p. 201—202° (decomp.), was obtained by similar condensation of γ-resorcylic acid (7 g.) with acetoacetic ester (6 g.) and sulphuric acid. There was no depression of the m. p. when this was mixed with the 8-acid obtained in the carboxylation reaction. This acid gives a blue colour with alcoholic ferric chloride; the 6-carboxylic acid gives a red colour. Some decarboxylation of the γ-resorcylic acid or of 7-hydroxy-4-methylcoumarin-8-carboxylic acid occurred during the condensation since 7-hydroxy-4-methylcoumarin (2 g.) was also isolated.

The crude 6-acid obtained in a carboxylation reaction carried out at 150° was contaminated with a small amount of resorcinol-2 : 4-dicarboxylic acid, m. p. 312° (Found: C, 48·5; H, 3·2. Calc. for $C_8H_6O_6$: C, 48·5; H, 3·0%), separated by taking advantage of its low solubility in acetone. This experiment gave the 8- (16·1 g.) and 6-carboxylic acid (10·5 g.) and resorcinol-2 : 4-dicarboxylic acid (1 g.). In a carboxylation at 180° the acid product (29·3 g.) consisted entirely of 8- and 6-acid (22·2 and 7·1 g. respectively).

When the 8-carboxylic acid (5 g.) was heated under reflux with 20% sodium hydroxide solution (20 c.c.) for 2 hours, the product consisted of γ-resorcylic acid (1 g.), resorcinol (1·2 g.), and 7-hydroxy-4-methylcoumarin (0·5 g.).

Separation of β- *and* γ-*Resorcylic Acid by Ion-exchange Chromatography.*—*Resin columns.* For preliminary experiments on a small scale, columns of the type described by Djurfeldt and Samuelson (*Acta Chem. Scand.*, 1950, **4**, 165) were employed. The bed of resin, 0·5 ml. in

volume (4·0 × 0·4 cm.), was supported between two glass-wool plugs. For separations on the gram-scale, a larger column with a bed-volume of approx. 20 ml. (12 × 1·4 cm.) was used. A polyethylene float was used in the column to prevent disturbance of the upper layers of the resin. During a separation the effluent from the column was collected in 10-ml. fractions, by a Shandon automatic fraction collector.

For the greater part of this work the weakly basic resin Amberlite XE-76 (supplied by the Rohm and Haas Co.) was employed. The behaviour of three other anion-exchange resins, Amberlite IRA-400 (Rohm and Haas Co.), De-Acidite B and De-Acidite E (Permutit Co. Ltd.) was also examined. In each case the particle diameter of the resin was 150—250 μ. Before use the resins were treated with N-hydrochloric acid and N-sodium hydroxide to remove any soluble matter. They were then converted into the chloride form with N-hydrochloric acid and washed to remove excess of regenerant.

Analysis of column effluent. Paper chromatography provided a convenient method of qualitative analysis. The procedure adopted was similar to that used by Bray, Thorpe, and White (*Biochem. J.*, 1950, **46**, 271). The chromatograms were developed with butanol–acetic acid and after drying were sprayed with a 0·2% solution of ferric chloride in 95% ethyl alcohol.

FIG. 1. *Apparatus for qualitative analysis of column effluent.*

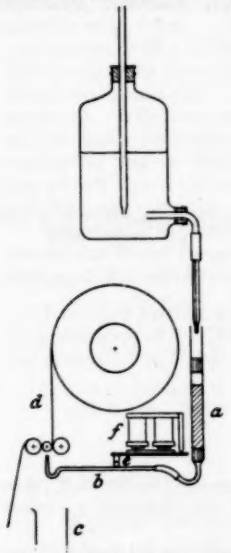
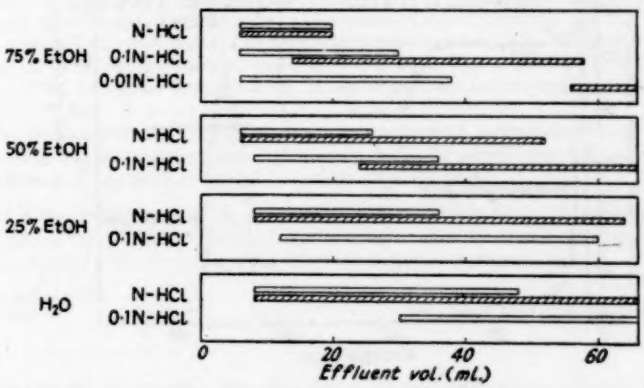


FIG. 2. *Effect of eluant. Open rectangles, β-resorcylic acid; hatched rectangles, γ-resorcylic acid.*



For the examination of the effluent from the small columns a procedure similar to that described by Drake (*Nature*, 1947, **160**, 602) was used. The apparatus is shown in Fig. 1. The effluent from the column (*a*) passed through a glass cannula (*b*) approx. 15 cm. in length and was collected in a receiver (*c*). A strip of Whatman No. 1 paper (*d*), 7 cm. wide, was moved past the tip of the cannula by rubber rollers at approx. 0·5 cm. per minute. The tip of the cannula was normally prevented from touching the surface of the paper by a metal bar (*e*). At intervals of 4 minutes the metal bar was raised momentarily by an electromagnet (*f*) operated through a time-switch. This allowed a drop of the column effluent from the glass cannula to be collected on the paper strip, about 1 cm. from the edge. At the end of an experiment, the paper was inserted in the spool of a photographic developing tank which was allowed to stand in a Petri dish containing butanol–acetic acid. After approx. 20 minutes, the paper strip was removed from the spool, dried, and sprayed with ferric chloride solution.

For qualitative analysis of the 10-ml. fractions from the larger column, 0·02-ml. samples from the different fractions were placed at 3-cm. intervals on sheets of Whatman No. 1 paper, and the chromatogram developed with butanol–acetic acid, Williams and Kirby's ascending method (*Science*, 1948, **107**, 481) being used.

For quantitative analysis of fractions from the large column, ultra-violet absorption was measured at 2940 and 3060 Å with a Beckman Model DU Spectrophotometer. Aliquot samples from the different fractions were diluted with water and ethyl alcohol to a suitable final concentration of the resorcylic acid and an ethyl alcohol concentration of 3·0%. The extent of cross-contamination in the intermediate fractions could be estimated from the ratio of the optical densities at 2940 and 3060 Å. A constant value for this ratio in samples from consecutive fractions indicated the presence of a single component.

Aqueous eluants. Preliminary experiments showed that both resorcylic acids were readily absorbed by Amberlite XE-76 in the chloride form and that they could be eluted with dilute acid or alkali. In all cases the β-acid appeared to be eluted preferentially. Alkaline eluting agents were however unsuitable owing to the instability of the resorcylic acids therein. The acids were therefore eluted with hydrochloric acid solutions. In a typical experiment, a solution containing 2·65 g. of the mixture of resorcylic acids in 500 ml. of water was passed through the 20-ml. column of Amberlite XE-76 in the chloride form at 5 ml. per minute. The β-resorcylic acid was then eluted with 1300 ml. of 0·1N-hydrochloric acid at the same flow rate, the effluent being collected in 10-ml. fractions. When the concentration of hydrochloric acid was increased to 0·5N, γ-resorcylic acid was eluted. A total volume of 1000 ml. of 0·5N-hydrochloric acid was passed through the column, but the γ-resorcylic acid was not completely removed. Fractions

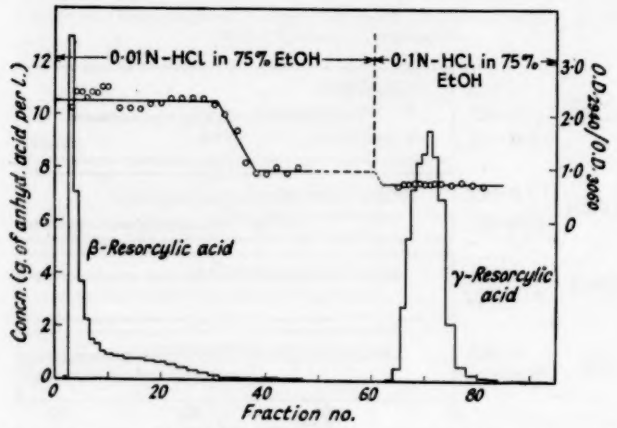


FIG. 3. *Separation of β- and γ-resorcylic acid.*

1—100 were combined and extracted with ether. On evaporation of the extract, pure β-resorcylic acid was obtained (0·88 g.). γ-Resorcylic acid (1·10 g.) was obtained by ether-extraction of fractions 135—235.

Non-aqueous eluants. Although a good separation of the two resorcylic acids was achieved by the method described above, large volumes of eluant were required to remove the acids from the column. It was considered that non-aqueous eluting agents would be more satisfactory since the solubility of the acids would be increased and they could be eluted at a higher concentration. In addition the presence of the organic solvent might result in more favourable distribution coefficients. Preliminary experiments were carried out with hydrochloric acid in mixtures of water with methyl alcohol, ethyl alcohol, *n*-butyl alcohol, acetone, or dioxan. It was confirmed that the presence of the organic solvent markedly reduced the volume of eluant required.

Use of solutions of hydrochloric acid in different mixtures of ethyl alcohol and water as eluting agents was examined in detail. The apparatus for small-scale experiments described above was employed. The column contained a 2-ml. bed of Amberlite XE-76 in the chloride form. A solution of 0·1 g. of the resorcylic acid mixture in 50 ml. of water was passed through the column which was then washed with 10 ml. of de-ionised water. The eluant was passed through the column at 0·5 ml. per minute. The results obtained are shown diagrammatically in Fig. 2. In general, for a given acid concentration, the volume of solution required to elute the resorcylic acids decreased as the proportion of alcohol in the solvent increased. Similarly, for a given alcohol concentration, the volume of eluant required decreased as the concentration of acid increased. It appears from Fig. 2 that 0·01N-hydrochloric acid in 75% (v/v) ethyl alcohol

would be suitable for the elution of the β-resorcylic acid and 0·1N- or N-hydrochloric acid in 75% (v/v) ethyl alcohol for the elution of the γ-resorcylic acid.

The use of these eluting agents for the separation of gram quantities was examined, with the 20-ml. column of Amberlite XE-76. A solution of 1·50 g. of the resorcylic acid mixture in 500 ml. of water was passed through the column at approx. 1·0 ml. per minute. The β-acid was then eluted with 0·01N-hydrochloric acid in 75% ethyl alcohol at 1·5 ml. per minute (total volume, 600 ml.). γ-Resorcylic acid was then eluted with 0·1N-hydrochloric acid in 75% alcohol at the same flow rate. The concentrations of the two resorcylic acids in the different fractions of the effluent are shown in Fig. 3 which also shows the ratio of optical densities (O.D.) of the different fractions at 2940 and 3060 Å. It will be seen from Fig. 3 that the β-resorcylic acid is contained in the first 350 ml. of effluent. The different value for the optical density ratio in the next 250 ml. of effluent indicates the presence of a third component. The presence of this additional component, probably resorcinol-2 : 4-dicarboxylic acid, was confirmed by paper chromatography; the R_F value was different from that of the β- and γ-resorcylic acids and a reddish-pink colour was obtained with ferric chloride solution. The γ-resorcylic acid was removed from the column in approx. 200 ml. of the 0·1N-hydrochloric acid. The resorcylic acids and the third component were isolated from the effluent by bulking the appropriate fractions, removing most of the alcohol by distillation *in vacuo*, and extracting the remaining solution with ether. The yields of β- and γ-resorcylic acid were 0·57 and 0·75 g. respectively, and approx. 0·02 g. of the third component was isolated. The m. p. of samples of the two acids which had been dried at 10^{-4} mm. over phosphoric oxide were β- 224° (corr.), γ- 171° (corr.) (both, rapid heating). The titration curve of β-resorcylic acid showed inflexions at pH 6 and about 10. γ-Resorcylic acid showed a single inflexion. The ultra-violet absorption spectra of the two acids, determined with a Beckman Model DU Spectrophotometer, for aqueous solutions containing approx. 0·02 g. of acid per l., showed max. at: β-, 2490 (log ε 4·00) and 2920 (log ε 3·66); γ-, 2460 (log ε 3·79) and 3060 Å (log ε 3·49), in agreement with Cartwright, Jones, and Marmion (*loc. cit.*).

Behaviour of different ion-exchange resins. Small-scale experiments with Amberlite IRA-400, De-Acidite B and De-Acidite E in the chloride form and approx. 0·1 g. of mixed resorcylic acids indicated that equally satisfactory separations could be achieved with them.

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672. *The Separation of Isotopes by Fractional Distillation. Part I. Fractionating Columns for the Enrichment of the Heavy Isotopes of Oxygen in Water.*

By I. DOSTROVSKY, D. R. LLEWELLYN, and B. H. VROMEN.

The construction and operation of a number of fractionating columns designed for the enrichment of the heavy isotope of oxygen in water are described. One is capable of producing, per day, 200 ml. of 0·6% $H_2^{18}O$, or 50 ml. of 1·7% $H_2^{18}O$, or 20 ml. of 3·2% $H_2^{18}O$. Another, operating as a second stage, has produced 10 ml. of 12% $H_2^{18}O$ per week.

FRACTIONAL distillation was one of the earliest methods applied to the enrichment of isotopic mixtures, though with only limited success. However, recent advances in both the theory and the technique of fractionation seemed to justify re-examination of the method. Separation of the stable isotopes of oxygen is of particular interest because oxygen is one of the few light elements without a long-lived radioactive isotope suitable for tracer studies.

Normal oxygen consists of a mixture of ^{16}O, ^{17}O, and ^{18}O in the approximate proportions 2500 : 1 : 5, from which it appears that ^{18}O is more easily separated from ^{16}O, because of its greater mass and abundance, than is ^{17}O. Most standard methods have been

employed to investigate their separation, such as electrolysis, chemical exchange, gaseous diffusion, and fractional distillation. Of these, thermal diffusion has been the most effective, but although 99% ^{18}O was obtained by this method, the yield was only 250 c.c. of gaseous oxygen after $1\frac{1}{2}$ years (Clusius, Dickel, and Becker, *Naturwiss.*, 1943, **31**, 210). This method is not very suitable for producing large quantities of water with sufficient ^{18}O content for chemical and biological tracer work.

The enrichment of ^{18}O and deuterium in water by fractional distillation has been achieved by a number of investigators. Huffman and Urey (*Ind. Eng. Chem.*, 1937, **29**, 531) describe the detailed working of a fractionating column, consisting of alternate stationary and rotating cones, with which they were able to produce 200 c.c. of water containing 0·85 atom-% ^{18}O; Watson (see *J.*, 1937, 1969) built a still which produced water with an increased density of 700 parts per million, but only part of this increase was due to ^{18}O; Brodski, Alexandrovitsch, and Skarra (*Acta Physicochem. U.R.S.S.*, 1937, **7**, 469) report the use of a 200-cm. column; Winter, Carlton, and Briscoe (*J.*, 1940, 131) produced water 200 parts per million heavy in ^{18}O, and Thode, Smith, and Walkling (*Canad. J. Res.*, 1944, **22**, *C*, 127), using three columns in cascade, produced 150 c.c. of water enriched 6·5-fold in ^{18}O (1·3%), in 120 days.

In this paper we describe the construction and operation of a number of improved fractionating columns designed for the enrichment of the heavy isotopes of oxygen in water. These columns have been in operation for several years and some of them are capable of producing, per day, 200 ml. of 0·6% $H_2{}^{18}O$ or 50 ml. of 1·7% $H_2{}^{18}O$ or 20 ml. of 3·2% $H_2{}^{18}O$. Even when the times necessary to reach these enrichments (see below) are taken into account it will be seen that this represents a considerable improvement over earlier columns. Several of these columns have been operating with efficiencies equivalent to between 400 and 600 theoretical plates.

In the separation of liquids of very similar boiling point, such as isotopic mixtures, by fractionation or chemical exchange, several problems arise which are not met in the more usual industrial and laboratory operations. These are derived from the small value of the unit process separation factor α, and in most practical cases from the very small concentration of the desired isotopic species in the starting material. The small value of α leads to the use of columns of very high efficiency which also means columns of large physical dimensions. This in turn creates problems of length of time required to reach concentrations suitable for production, a point which is hardly considered in industrial columns.

The theory of fractionation, as applied to the separation of isotopes, has been developed by Cohen (*J. Chem. Phys.*, 1940, **8**, 588) and by Dostrovsky, Gillis, and Llewellyn (*Bull. Res. Council, Israel*, 1951, **1**, 120; Farkas Memorial Volume, in the press) and has permitted the rational design and operation of columns for this purpose. The present paper is devoted mainly to those features of design and construction which lead to efficient and dependable apparatus; for not the least exacting requirement of any apparatus for isotopic enrichment is long-term dependability and steadiness of operation.

Recent research has resulted in the development of a number of packing materials possessing a high efficiency with a large through-put. One such is Dixon's wire-gauze packing (*J. Soc. Chem. Ind.*, 1949, **68**, 88). Its suitability for use in columns for isotopic work was demonstrated by Dostrovsky, Hughes, and Llewellyn (*Nature*, 1946, **158**, 164; 1948, **161**, 858). It shows a linear relation between the height of equivalent theoretical plates and flow, as required by the theory (Dostrovsky, Gillis, and Llewellyn, *op. cit.*), the height equivalent to a theoretical plate (H.E.T.P.) being $0{\cdot}04\ \frac{\text{cm. per plate}}{\text{l. per day}}$ for a $3\frac{1}{2}$-in. column. Thus for a flow of 25 l. per day the H.E.T.P. of such a column is 1 cm.

Basically three modes of operation are possible and all have been used. In the first (mode 1), the continuous process, the feed stock (usually normal distilled water) is introduced at a constant rate at the top of the column and passes through the packed section to the boiler. Apart from the relatively small quantity of water withdrawn from the boiler as product, all the water is returned to the foot of the column as steam. The steam passes up the packed section to the condensers and the condensate flows to a reservoir and is

discarded (see Fig. 1). The second mode of operation (mode 2) is a batch process. The same arrangement is used as in the continuous process but with a relatively large boiler and with no production taken until the contents of the boiler reach the desired concentration. At this point most of the boiler content is taken as production. The third mode of operation (mode 3), also a batch process, is shown schematically in Fig. 2. Steam from the boiler, after passing through the packed section, is condensed into the reservoir where it displaces an equal volume of water into the top of the column. It follows from the general theory (Dostrovsky, Gillis, and Llewellyn, *loc. cit.*) that the total time necessary to produce a given amount of enriched water is much the same whether the first or the second mode is adopted. The first mode of operation has, however, an obvious advantage which may be of decisive importance in certain circumstances, namely, that, should a breakdown occur in the operation, the material already produced is at least saved. The third mode of operation enjoys the great advantage of simplicity, as no direct flow control is needed. The flow is entirely determined by the heat input to the boiler. Another advantage is that the total amount of water in the system is fixed and so this method is suitable when starting from enriched material. A disadvantage of this mode is that for a

FIG. 1.

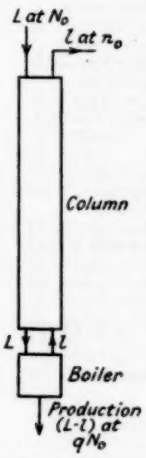


FIG. 2.

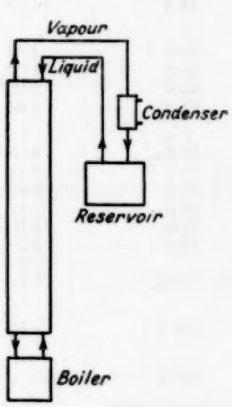
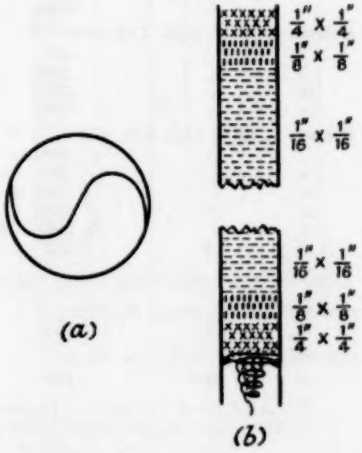


FIG. 3.



given column the enrichment is always less than in the other methods of operation (cf. Dostrovsky, Gillis, and Llewellyn, *loc. cit.*). This mode can be rendered continuous by removing only a small fraction of the boiler water at a time, and adding an equal volume slowly to the reservoir (mode 3*a*).

The design of the boiler depends on the type of operation required. Those intended for batch operation have a relatively large working volume and are of conventional laboratory design, consisting of a flask fitted with internal heater or external heating mantle.

Boilers intended for continuous production have the minimum working volume consistent with the desired boil-up rate, an essential requirement which follows from consideration of the rate of enrichment. These are most conveniently heated by steam, and a boiler with a boil-up rate of 10 l. of water per hour with a working volume of less than 100 c.c. was used. In electrically heated boilers the heat input is balanced against the inflow of water by a device which maintains a constant water level.

Columns about 1" in diameter were constructed of Pyrex and thermally insulated by vacuum-jackets (Dostrovsky and Jacobs, *Chem. and Ind.*, 1947, 627), while the larger ones, of 3" diameter, were fabricated from copper and insulated with two layers of fibre-glass pipe lagging with compensating heaters between the layers. The condensers were all of the usual design, consisting simply of two water-cooled spirals connected in series. Vapour from the column condensing on these spirals could be led to the distillate reservoir or

returned to the top of the column. The columns were operated under reduced pressure in order to take advantage of the correspondingly higher values of α.

In designing the stills it was borne in mind that it would be necessary for them to operate for long periods (many months) without continuous attention, and it was necessary to safeguard the equipment from damage and the enriched water from loss consequent upon water or electricity failure or breakdown in parts of the apparatus. Steam-heated stills were designed to be unaffected by failures of a few hours' duration. The flow of feed stock was kept constant by means of an automatic flow controller described elsewhere (cf. Dostrovsky and Llewellyn, *J. Sci. Instr.*, 1948, **25**, 137). Failure of the flow of feed stock in these columns was made to operate magnetic valves which caused the stills to function under total reflux by returning the distillate to the top of the column.

Some results obtained are shown in the annexed Table.

Run	Mode	Mean pressure (mm.)	Flow (l./day)	Enrichment	Production
Column C, 25 ft. high, 3½ in. diam.					
i	1	259	51·7	3·22	150 c.c./day
ii	,,	259	50·1	4·10	100 ,,
iii	,,	271	37·9	8·26	30 ,,
iv	,,	274	36·7	11·23	20 ,,
v	,,	265	33·3	11·20	20 ,,
Column A, 30 ft. high, 3 in. diam.					
i	1	290	95·5	4·07	150 ,,
ii	,,	290	92·5	4·52	115 ,,
iii	,,	290	95·5	5·25	60 ,,
iv	,,	290	92·5	5·98	30 ,,
Column B, 50 ft. high, 3 in. diam.					
i	1	290	57·5	3·08	200 ,,
ii	,,	290	57·5	3·74	150 ,,
iii	,,	290	57·5	5·05	100 ,,
iv	,,	290	57·5	8·52	50 ,,
v	,,	290	57·5	16·0	20 ,,
vi	2	290	84·0	3·2	2 l./day †
				2·3	3 ,,
				1·8	3 ,,
Column D, 12 ft. high, ¾ in. diam.					
i	3	200	560 ‡	1·93	500 c.c. in 24 wks.
Column E, 25 ft. high, 1 in. diam.					
i	3a*	160	300 ‡	60	10 c.c./wk.

* Feedstock, 1·7% $H_2{}^{18}O$. In other cases, normal water. ‡ C.c./hour.
† After one run of 8 weeks. The product includes some drainage from the column.

The columns were designed for the production of $H_2{}^{18}O$ and the conditions with respect to HDO production were far from optimal. Under conditions *C*(iv) a deuterium enrichment of 70 ± 5 times the normal value (HDO ~2·5%) was obtained and under conditions *C*(v) an enrichment of 78 ± 4 was obtained.

Some of the results in this Table indicate non-optimal operation of the column. These are runs which were made to test theoretical formulæ and to determine various parameters. A further discussion of these and related questions will appear in subsequent papers.

Experimental

Description of Columns.—The packing in all the columns described in this paper was made from 100-mesh phosphor-bronze gauze in the form of cylinders $\frac{1}{16} \times \frac{1}{16}$" divided down the middle by an S-shaped partition. Fig. 3*a* shows a cross-section of one of these cylinders. At each end of the packed section there were layers of larger packing, $\frac{1}{8} \times \frac{1}{8}$ and $\frac{1}{4} \times \frac{1}{4}$" (see Fig. 3*b*, which also shows the method of support of this packing in the column).

The columns themselves and all their connections were made of copper, except for some of the small-diameter columns which were of glass.

As with other types of packing, the material used in our columns functioned most efficiently if thoroughly wetted at the beginning of the operation. In columns designed for continuous operation this was achieved by initially maintaining a rate of flow greater than the rate of boiling, until the flooding was complete. The flow was then reduced until, after deflooding,

a correct balance was restored. In batch columns the flooding was effected by slowly introducing excess of water directly into the boiler. The columns were then deflooded by gradual removal of the surplus water.

(a) *The 3″ × 30′ Electrically Operated Column.*—This was designed for the three modes of operation and is shown diagrammatically in Fig. 4. It has only been used, however, for continuous production.

The column was made from 3″-bore 16-gauge copper pipe and had a total length of 31 ft. A 30-ft. length of the column was filled with 100-mesh phosphor-bronze packing (2″ at each end $\frac{1}{4} \times \frac{1}{4}$″, followed by 6″ at each end $\frac{1}{8} \times \frac{1}{8}$″, and the remainder with $\frac{1}{16} \times \frac{1}{16}$″). The remaining length contained a reflux condenser (11) and the outlets of the feed (5) and flood (6) pipes, and was connected at the top to the main condensers (12 and 13) from which a pipe (23) led to a reservoir (14) situated on the level of the base of the column. The water supply to the reflux condenser (11) and to the main condensers (12 and 13) was controlled by separate valves

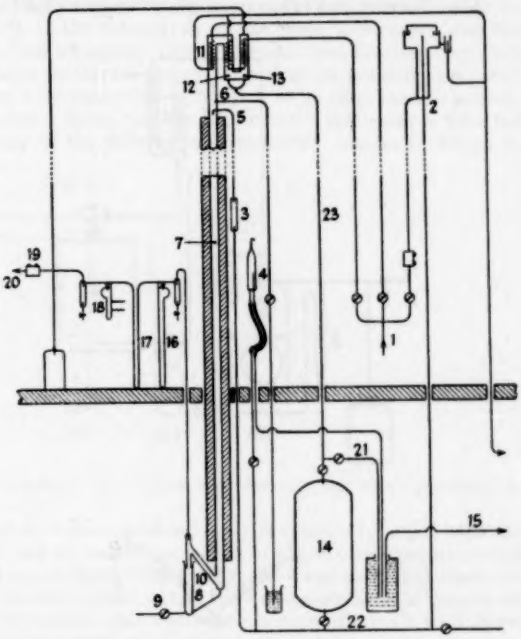


FIG. 4.

1, *Mains water supply.*
2, *Distilled water supply.*
3, *Flowmeter.*
4, *Controlling head operated by servo-mechanism of recorder controller.*
5, *Feed pipe.*
6, *Flood pipe.*
7, *Column.*
8, *Boiler.*
9, *Outlet for product.*
10, 1″ *Copper tube between boiler and column.*
11, *Reflux condenser.*
12, 13, *Main condensers.*
14, *Reservoir.*
15, *Waste distillate.*
16, *Boiler manometer.*
17, *Differential manometer.*
18, *Manostat.*
19, *Magnetic valve.*
20, *Pumping line.*

(1). From the reservoir (14) one pipe (21) led to waste, and another (22) connected with the feed pipe (5). Distilled water from the still (2) could be fed directly through a flowmeter (3) to the top of the column.

The flowmeter was of the thermal type, as described by Dostrovsky and Llewellyn (*loc. cit.*). A mechanical servo-mechanism kept the bridge balanced by varying the head of the water (4) flowing into the column. A commercial instrument was used for recording the flow.

Thermal insulation was provided by fibre-glass pipe lagging, $2\frac{1}{4}$″ thick, built in two layers with an electric heater between them. The input to this heater was controlled so as to compensate for heat losses from the column. Thermocouples were provided throughout the length of the insulation to ensure the correct adjustment of the compensating heater.

Water flowing down the column was led through a glass tube to the bottom of the boiler (8) which was made of a $2\frac{3}{4}$″-diam. Pyrex tube, 24″ long, containing four 1-kw tubular heaters of the type used in domestic fires. These were supported and electrically connected by two $\frac{1}{2}$″ glass-sleeved copper rods passing through a rubber bung at the top of the boiler. The vapour was returned to the column through a 1″ copper pipe (10), also passing through the bung. Samples of water could be removed from the boiler through a side tube and valve (9).

The boiler had a working volume of 200 ml. of water and it was essential to keep this volume

sensibly constant. This was achieved by incorporating a level-controlling device which consisted of a thermocouple, surrounded by a small low-voltage heater wound on a silica core and inserted in a silica tube of $\frac{1}{4}''$ diameter, closed at one end and extending two-thirds of the way down the boiler. The temperature indicated by the thermocouple depends on its position relative to the level of the water. With the water slightly above the predetermined level the temperature recorded was about 300°; with the water below this level the temperature rose sharply to 400°. The thermocouple was connected to a commercial pyrometer controller set at 350°, which below this temperature short-circuited a 2·5-ohm resistance in series with the main heater elements, whereas above this temperature the resistance was in the circuit. In this way the heat input was varied to maintain approximately constant water level. This arrangement compensated for changes in heat input due to line-voltage fluctuations and other causes, and also obviated the necessity for close matching of the constant feed rate with the boiler current. The boiler current was recorded on a 3-point recorder together with the current to the commercial still and the line voltage.

A connection was taken from the 1″ copper pipe (10) to the manometer (16) and differential

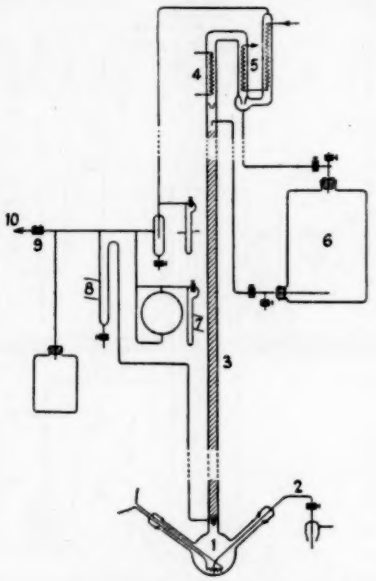


FIG. 5.

1, *Boiler.*
2, *Outlet for product.*
3, *Column.*
4, *Reflux condenser.*
5, *Main condenser.*
6, *Reservoir.*
7, *Manostat.*
8, *Differential manometer.*
9, *Magnetic valve.*
10, *Pumping line.*

manometer (17). The other side of this differential manometer was connected to the top of the condenser (13), to the manostat (18), and to the vacuum line (20). The manometers were of the usual glass U-tube design, and the manostat had two tungsten contacts in the closed arm. These contacts operated an electromagnetic valve situated in the vacuum line between the pump and the column. In this column no provision was made for dealing with breakdowns of electric power supply, but numerous safety devices were incorporated into the still which stopped the operation in the event of any failure of mains-water supply, boiler heating, or flow of feed stock, and suitable alarm signals were provided to indicate serious deviations from the desired running conditions.

(b) *The 3″ × 50′ Electrically Heated Still.*—This still was very similar to the 30-ft. still previously described. The flow-control system was self-contained and fed a constant flow of water to one end of a 40-ft. U-tube, the other end of which entered the column above the packing.

The boiler was all-metal and heated by three 1·5-kw. kettle-heaters. The capacity of this boiler was reduced by filling most of the free space with brass rod, and the level-sensitive element was designed to switch the top heater. Each heater had its own emergency cut-out and no other safety device on the boiler was necessary.

(c) *The $3\frac{1}{2}''$ × 25′ Steam-heated Still.*—Like stills (A) and (B), this too was designed for con-

tinuous operation. The use of steam from a large-capacity boiler for heating both the still-boiler and the insulating jacket afforded some protection against extended power cuts. In addition, a small auxiliary generator was used to provide an emergency power supply for maintaining the flow and the various control and safety circuits.

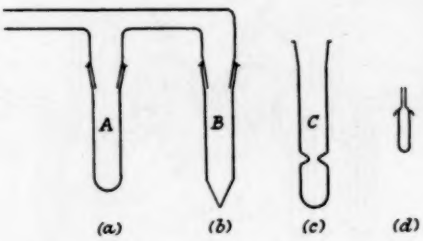
The still-boiler was of tube type, with the steam outside the tubes, and made of copper. Its working volume varied from 30 to 50 ml. and was capable of boiling up to 10 l. of water per hour.

In other respects this column was closely similar to (a) and (b).

(d) *The* $\frac{3}{4}''$ × 12′ *Electrically Heated Still.*—This column (see Fig. 5) was designed for batch operation and was of glass. Thermal insulation was provided by sleeve-type vacuum-jackets containing three concentric aluminium reflectors (see Dostrovsky and Jacobs, *loc. cit.*) and a small compensating heater was wound directly on the column.

The boiler was made from a 750-ml. Pyrex flask fitted with two side arms, one carrying an 8-ohm nichrome-wire heater connected to a Variac transformer, and the other fitted with a syphon tube for withdrawal of samples. Vapou. reaching the top could be condensed either by the reflux condenser (and returned directly to the column) or by the main condensers, and the condensate led into the reservoir from which an equal volume of water was displaced and fed into the top of the column. It is desirable to have a reservoir as large as possible compared to the contents of the boiler. Reservoirs with capacities of 1—20 l. have been used in accordance with the amount of material available. From the top of the main condenser a tube led to the manostat, manometer, and one side of the differential manometer, similar in design to

FIG. 6.



that used in the 3″ column. The other side of the differential manometer was connected to the boiler.

The effects of mains-voltage fluctuations were minimised by a resistance in series with the boiler heater which was switched in and out of circuit by means of a hot-wire vacuum-switch actuated by contacts in the differential manometer. The arrangement was such that when the pressure difference decreased below the predetermined value, the extra resistance in the circuit was short-circuited, thereby increasing the boil-up rate until the pressure difference rose above the set value. In this way the average boil-up rate was maintained approximately constant.

The usual safety devices were incorporated. In addition a double-pole double-throw electronic relay was used as a change-over switch to connect the heater to a reserve battery in the event of mains failure.

(e) *The* 1″ × 25′ *Electrically Heated Still.*—This was similar to the $\frac{3}{4}''$ × 12′ still. The boiler was heated by an external mantle, which enabled the working volume to be reduced considerably, and the column was lagged with fibre-glass.

Isotopic Analysis.—Although all of our more recent isotopic analyses of water samples have been carried out mass-spectrometrically (cf. Dostrovsky and Klein, *Analyt. Chem.*, 1952, in the press; Cohn and Urey, *J. Amer. Chem. Soc.*, 1938, **60**, 679), earlier determinations were made by the pycnometric method to be described below. Because of the possible usefulness of this method where a mass spectrometer is not available and also because of the intrinsic interest of some of the techniques involved, a brief description is given.

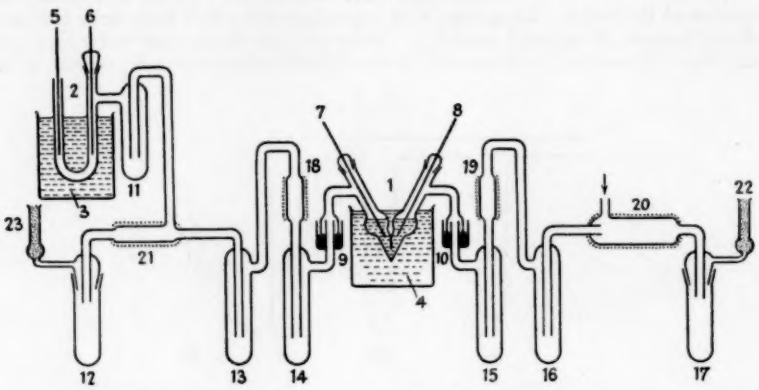
The pycnometers used were made of Pyrex glass or silica and were of the shape shown in Fig. 6*d*, with a capacity of 2—3 ml. In order to fill and empty these pycnometers it was convenient to have several tubes of the forms shown in Fig. 6*a*, *b*, and *c*. These tubes would be connected to a high-vacuum line by placing cone and socket together dry and sealing them by running Apiezon wax W 80 around the rim.

All tubes were normally kept completely immersed in chromic acid and before use were well washed with distilled water, thoroughly steamed internally with steam generated from potassium permanganate solution, and finally dried at the pump.

The pycnometer was cleaned externally after each measurement by holding it with tweezers in a stream of steam and was then inverted into a tube of shape *B* (cf. Fig. 6), attached to the high-vacuum line, and was then pumped dry. The vacuum was then broken, tube *A* (Fig. 6*a*) was removed and replaced by a similar tube containing the frozen sample of water. After a few minutes' pumping, the system was isolated from the pumps, the tube containing the pycnometer was surrounded by acetone–solid carbon dioxide, and the water sublimed from *A* to *B*. This process took 2—3 hours if the surface area of the ice was large and if a reasonable vacuum was attained, and trap *A* was kept de-iced by occasional immersion in ethylene glycol.

When distillation was complete, the system was pumped out for a few minutes, to remove most of residual gas, the freezing-bath was removed, and the ice allowed to melt. The vacuum was then broken, causing the water to flow into the pycnometer. A small bubble (less than 1 mm. in diameter) remained, due to residual gas. The pycnometer was then removed, inverted, and given a vigorous jerk to bring the bubble to the base of the capillary from where it was expelled

FIG. 7.



1, *Cell for heavy water.*
2, *Cell for normal water.*
3, 4, *Cooling tanks.*
5—8, *Nickel electrodes.*
9, 10, *Mercury seals.*
11—17, *Liquid-air traps.*
18, 19, *Purification combustion tubes.*
20, 21, *Main combustion tubes.*
22, 23, *Phosphoric oxide guard tubes.*

on immersion in a thermostat at 25°. After the pycnometer had been for 10 minutes in the thermostat, surplus water was removed from the top of the capillary by touching it with a filter paper, and after a further 5 minutes the pycnometer was wiped with three pieces of chamois leather and transferred to the micro-balance.

The thermostat was kept at constant temperature, within $\pm 0{\cdot}001°$, and a very rigorous schedule of time in the thermostat, sequence of wiping, and time in the balance before weighing was adhered to. With a pycnometer of 3-c.c. capacity results were reproducible within ± 2 p.p.m. The pycnometer was emptied after removal from the balance by inverting it, shaking it to displace the bubble at the base of the capillary, and then alternately pumping and breaking the vacuum while the pycnometer was inverted in tube *C*.

Determinations of two densities were taken on each sample, one being a total density as represented by the increased concentrations of ^{18}O and D, and the other after normalisation by electrolysis. In each case the water was purified by a double distillation, the first after addition of potassium permanganate and a little sodium, and the second after addition of a little phosphoric oxide. Each distillation was carried out at a slow rate under atmospheric pressure in an all-glass apparatus and each distillation was taken almost to dryness. To determine the total density, a small piece of sodium was added to the sample and 3 ml. were transferred to a clean dry trap *A*. The outlet was closed by a B24 stopper and the water was frozen by immersion in a solid carbon dioxide–acetone bath while the trap was held almost horizontal and rapidly rotated.

The remainder of the sample was converted into about 6N-sodium hydroxide by further additions of small pieces of sodium (cf. Dostrovsky and Llewellyn, *J. Soc. Chem. Ind.*, 1949, **68**, 208). It was then electrolysed in the apparatus described below, and the oxygen evolved was combined with purified hydrogen (from a cylinder). The resulting water (3 ml.) was treated with a crystal of silver nitrate and a little sodium, and after freezing was ready for vacuum-sublimation into the pycnometer as already described.

The apparatus for electrolysis and combustion is shown in Fig. 7, which is largely self-explanatory.

The cell for electrolysis of ordinary water was a large U-tube fitted with nickel electrodes, and presented no difficulty. In the cell for electrolysis of heavy water it was essential to keep the volume of water necessary to a minimum but at the same time to prevent boiling of the electrolyte and mixing of the gases while a reasonable current (say 3 amp. was passed). The design shown in Fig. 7 proved very satisfactory. With this cell, 5 ml. of water could be electrolysed down to ½ ml. at a current of 3 amp. (4·5 amp. could be used for the initial stages). There was slight mixing at the commencement of the electrolysis, but after a few minutes a heavy layer of sodium hydroxide solution seemed to form at the bottom of the cell and mixing was almost completely eliminated. However, a heated tube of platinised pumice was introduced into each line, followed by a trap cooled in solid carbon dioxide, thus ensuring that the oxygen and hydrogen were not contaminated as a result of unobservable mixing (*e.g.*, by solution of the gases).

The combustion chamber for the heavy hydrogen and normal oxygen (in the correct molecular ratio for H_2O), which was filled with platinised asbestos and heated to 300°, provided no difficulties. In the early stages a similar cell for burning heavy oxygen in excess of hydrogen was inclined to explode. The final device used was the combustion chamber just described but made much larger and filled with platinised and palladised pumice.

The authors express their gratitude to Professor E. D. Hughes, F.R.S., for his valuable advice and comments, to Dr. J. Gillis for helpful discussion during the preparation of this manuscript, and to Drs. C. A. Bunton and F.Klein for carrying out numerous mass-spectrometric analyses. One of them (D. R. Ll.) also acknowledges tenure of an I.C.I. Research Fellowship at University College, London.

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673. *The Separation of Isotopes by Fractional Distillation. Part II.* Determination of Parameters from Production Data. Value of the Unit Process Separation Factor for the* $H_2^{16}O$–$H_2^{18}O$ *System.*

I. Dostrovsky, J. Gillis, D. R. Llewellyn, and B. H. Vromen.

Application of the theory of fractional distillation to the data obtained in the production of enriched isotopic materials makes it possible to derive simultaneously the values for the unit process separation factor, α, and the effectiveness of the column for the system used. A graphical method is presented which facilitates the derivation of such information from experimental data. The values of the unit process separation factors for the systems $H_2^{16}O$–$H_2^{18}O$ and H_2O–HDO have been determined from the results of fractionation of water.

I. *Steady-state Operation of Fractionating Column for Isotope Separation.*—The theory of the steady-state operation of a packed column for isotope separation has been developed by Cohen (*J. Chem. Phys.*, 1940, **8**, 588; cf. N.N.E.S., Div. III, Vol. Ib) and the authors (*Bull. Res. Council, Israel*, 1951, **1**, 120; Farkas Memorial Volume, in the press). The

* Part I, preceding paper.

relevant equations, subject to assumptions and limitations discussed before by the authors (*loc. cit.*), are :

$$L\,\mathrm{d}N/\mathrm{d}z + k(N - \alpha n) = 0 \quad . . . . . (1.1)$$

$$l\,\mathrm{d}n/\mathrm{d}z + k(N - \alpha n) = 0 \quad . . . . . (1.2)$$

where z is measured from 0 at the head of the column to Z at its foot, $N(z)$, $n(z)$ are the mole fractions of the rarer isotope in the liquid and the vapour, respectively, at the distance z from the top of the column; L and l are respectively the downward rate of flow of liquid and upward rate of flow of vapour; k is a coefficient which determines the rate of transfer of isotope at the vapour–liquid interface; and α is the unit process separation factor of the rare isotope for the liquid–vapour system.

It is assumed that the mixture is dilute and obeys Henry's law, *i.e.*, at equilibrium $n = N/\alpha$ and the distance of the system from equilibrium conditions can be represented by $N - \alpha n$. The transfer between the phases is assumed to be proportional to this distance from equilibrium. The more exact form of the transfer law is irrelevant for concentrations below 10%, and if it transpires that the Raoult-like law and not this one is the more accurate for higher concentrations then all our results remain valid provided we replace throughout N and n by $RN/(1 - N)$ and $rn/(1 - n)$ respectively.

The boundary conditions for operation with liquid feed at the top of the column at constant conentration N_0 and with product taken from a finite boiler at the bottom are :

$$N(0) = N_0 \quad . . . . . (1.3)$$

and

$$L[N(Z) - \alpha n(Z)] + (\alpha - 1)\,ln(Z) = 0 \quad . . . . . (1.4)$$

The solution of equations (1.1) and (1.2), subject to conditions (1.3) and (1.4), is immediate and leads to

$$n(Z) = N_0 \frac{\dfrac{p}{\alpha - 1} + \dfrac{1}{\alpha}}{\dfrac{\alpha p}{\alpha - 1} + \dfrac{1}{\alpha(1 + p)} \mathrm{e}^{-\frac{kZ}{L}(\alpha - 1 + \alpha p)}} \quad . . . . . (1.5)$$

where we have written

$$p = (L - l)/l \quad . . . . . (1.6)$$

Now the concentration of rarer isotope in the boiler

$$= N_B \text{ (say)} = \alpha n(Z)$$

and so

$$N_B = N_0 \frac{\dfrac{\alpha p}{\alpha - 1} + 1}{\dfrac{\alpha p}{\alpha - 1} + \dfrac{1}{\alpha(1 + p)} \mathrm{e}^{-\omega z\left(1 + \frac{\alpha p}{\alpha - 1}\right)}} \quad . . . . . (1.7)$$

where we have written

$$\omega = k(\alpha - 1)/L \quad . . . . . (1.8)$$

The enrichment $q = N_B/N_0$

$$= \frac{\dfrac{\alpha p}{\alpha - 1} + 1}{\dfrac{\alpha p}{\alpha - 1} + \dfrac{1}{\alpha(1 + p)} \mathrm{e}^{-\omega z\left(1 + \frac{\alpha p}{\alpha - 1}\right)}} \quad . . . . . (1.9)$$

II. *Determination of Parameters from Steady-state Operation Data.*—For a given column the equation (1.9) determines q as a function of p. When $p = 0$ we get

$$q = \alpha \mathrm{e}^{k(\alpha - 1)z/L}$$

a result given by Cohen (*loc. cit.*). This, by analogy with Rayleigh's equation (*Phil. Mag.*, 1902, **4**, 521), suggests that we identify kZ/L with the number of transfer units.

In the case of isotope separation this number is for practical purposes equal to the number of theoretical plates in the column. The inverse proportion between this latter number and L is confirmed, for the type of packing used, by our experimental results (cf. section V) though it is known not to hold for some other types of packing.

It is worth considering what happens if we let $kZ/L \longrightarrow \infty$, *i.e.*, make the column infinitely efficient. Then (1.9) becomes

$$q = 1 + \alpha - 1/\alpha p \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2.1)$$

and this is the maximum enrichment attainable for the given value of α and p. An immediate practical application is that there is in general a limit beyond which it is not economic to extend the number of theoretical plates.

If we know the values of the enrichment corresponding to two or more sets of values of flow and production rates, we can, theoretically, deduce the values of α and kZ. The best technique for making this deduction will depend on the circumstances. If the value of L is the same in both production runs we may use tabulated values of (1.9) as a function of α, p, and kZ/L (cf. Dostrovsky, Gillis, and Llewellyn, Farkas Memorial Volume).

The use of the tables depends on the fact that a given pair of (p, q) values determines a relation between α and kZ/L, *i.e.*, a curve in the co-ordinate plane, α, kZ/L. From the intersection of two such curves we obtain the actual values of α and kZ/L. It should be emphasized that this method is only approximate and that the tables themselves, in so far as one depends on linear interpolation between parameter values, may at best give only a good approximation to the true values. The refinement of the approximate values to the degree of precision required by the circumstances may be effected by a trial-and-error use of equation (1.9). The limitation of the use of the tables to the case in which the different runs are taken with the same value of L is a substantial one, particularly as it may be technically difficult to keep L constant over long periods of time. The graphical method described below in section III is not subject to this limitation.

III. *Graphical Method.*—This method is approximate and is valid only for small values of $(\alpha - 1)$ and p. However the restriction is unimportant since the most useful practical cases are still covered. We start from equation (1.9) and write

$$x = \alpha p/(\alpha - 1), \qquad y = kZ(\alpha - 1)/L, \qquad \alpha(1 + p) \sim 1$$

Then

$$q \sim \frac{x + 1}{x + e^{-y(1+x)}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3.1)$$

For each of a range of values of q we plot, on the same sheet, $\log_{10} y$ against $-\log_{10} x$. For this purpose we write

$$Y = \log_{10} y \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3.2)$$
$$X = \log_{10} x$$

and denote the curve of Y against X by Γq.

Values of (X, Y) for a set of values of q are tabulated in the Appendix. The general character of the curves Γq is shown in Fig. 1.

Suppose now that we are given two sets of values of L and p with the corresponding values of q. Let us denote these by (L_1, p_1, q_1) and (L_2, p_2, q_2). Substituting each of these sets in turn in equation (1.9) we obtain a pair of equations for kZ and α. These can be solved graphically by means of the curves Γq. We seek two points (X_1, Y_1) and (X_2, Y_2) with the following properties:

(*a*) (X_1, Y_1) lies on Γq_i $(i = 1, 2)$
(*b*) $X_2 - X_1 = \log_{10} (p_1/p_2)$
(*c*) $Y_2 - Y_1 = \log_{10} (L_1/L_2)$

When these have been found, *e.g.*, by a technique to be described below, we may write

$$(\alpha - 1)/\alpha = p_1 \,.\, \text{antilog}_{10}\, X_1 = p_2 \,.\, \text{antilog}_{10}\, X_2 \quad . \quad . \quad . \quad (3.3)$$

thus determining α.

Then

$$kZ = L_1/(\alpha - 1) \,.\, \text{antilog}_{10}\, Y_1 = L_2/(\alpha - 1) \,.\, \text{antilog}_{10}\, Y_2 \quad . \quad (3.4)$$

The only approximation involved is $\alpha(1 + p) \sim 1$. Moreover this is not a very serious one since the term in question multiplies exp.$\{[-kZ(\alpha - 1)/L] \,.\, [(1 + \alpha p/(\alpha - 1)]\}$ which in practice is always quite small, and particularly so when $(\alpha - 1)$ or p is large enough for $\alpha(1 + p)$ to differ significantly from 1.

A simple technique for locating the points (X_1, Y_1), (X_2, Y_2) is as follows: Take a set-square, preferably transparent, ABC, with its right angle at B. Lay this square with B at the origin of co-ordinates O, and with BA and BC along the axes OX and OY respectively. Now mark off BQ_1, along BA equal to $\log_{10}(p_1/p_2)$ in units of the X-scale. Similarly mark off BQ_2 from BC equal to $\log_{10}(L_1/L_2)$ in units of the Y-scale. Set the triangle keeping BA and BC parallel to OX and OY, with A to the left or right of B according as $p_1 >$ or $< p_2$, and with C above or below B according as $L_1 >$ or $< L_2$. Now

FIG. 1.

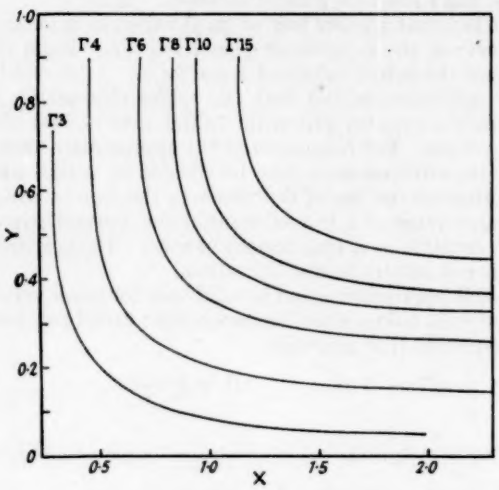
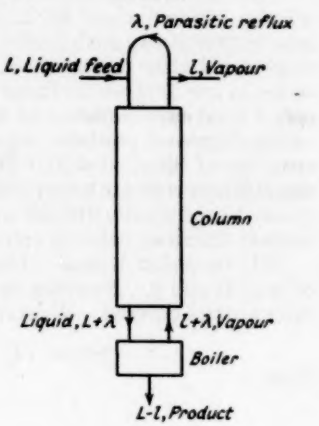


FIG. 2.



move the triangle parallel to itself until Q_1 lies on Γq_1, and Q_2 on Γq_2. The positions of Q_1, Q_2 will be the points (X_1, Y_1), (X_2, Y_2) required.

IV. *Effect of Condensation in the Column.*—In many practical systems, a part of the vapour may be unavoidably condensed in the upper part of the column, either through heat loss or by the feed liquid if the latter is below the boiling point. This effect will lead to rates of liquid and vapour flow within the column greater than feed and distillate rates respectively. Let λ be the additional flow (both liquid and vapour) in the column arising from this effect. The situation is described diagrammatically in Fig. 2.

Equations (1.1, 1.2) remain valid except that L, l are to be replaced by $L + \lambda$, $l + \lambda$ respectively. The boundary conditions are now:

(i) Material balance in boiler:

$$(L + \lambda)N(Z) - (l + \lambda)n(Z) = (L - l)\,\alpha n(Z) \quad . \quad . \quad . \quad . \quad (4.1)$$

(ii) Overall material balance:

$$LN_0 - ln(0) = (L - l)\,\alpha n(Z) \,. \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4.2)$$

The assumption underlying (4.2) is that the outgoing vapour has the same composition as that rising from the top of the packing. Another possible assumption could be that the condensate is in equilibrium with the uncondensed vapour, *i.e.*, that there is a slight

stripping of the uncondensed vapour and that therefore the concentration of heavy isotopes in the distillate leaving the column is slightly below $n(0)$. Both of these extreme cases have been worked out in detail and it transpires that there is no significant difference between the two values of q. For simplicity we shall use equation (4.2) as it stands.

The solution of the differential equations with these boundary conditions leads to :

$$q = \alpha n(Z)/N_0$$

$$= \frac{1 + \frac{\alpha}{\alpha - 1} \cdot \frac{L - l}{l + \lambda}}{\frac{l}{\alpha L} e^{-\omega Z} + \frac{\alpha}{\alpha - 1} \cdot \frac{L - l}{l + \lambda} \cdot \frac{L + [\alpha - 1)/\alpha]\lambda}{L}} \quad . \quad . \quad . \quad . \quad (4.3)$$

where

$$\omega Z = \{kZ/(L + \lambda)\}\left\{\alpha - 1 + \frac{\alpha(L - l)}{l + \lambda}\right\} \quad . \quad . \quad . \quad . \quad (4.4)$$

We now write $p = (L - l)/l$, *i.e.*, the *observed* reflux ratio. Then (4.3) becomes

$$q = \frac{1 + \frac{\alpha}{\alpha - 1} \cdot \frac{p}{1 + \lambda/l}}{\frac{1}{\alpha(1 + p)} e^{-\omega Z} + \left[1 + \frac{\alpha - 1}{\alpha(1 + p)} \cdot \frac{\lambda}{l}\right] \frac{\alpha}{\alpha - 1} \cdot \frac{p}{1 + \gamma/l}} \quad . \quad . \quad . \quad (4.5)$$

The effect of the parasitic reflux γ on the observed enrichment q may be in either direction depending on the position of $(L + \lambda)$ with respect to the optimal flow (cf. Dostrovsky, Gillis, and Vromen, *Bull. Israel Research Council*, Vol. II, in the press).

We also write

$$p' = (L - l)/(l + \lambda) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4.6)$$

and

$$q' = \frac{1 + \frac{\alpha p'}{\alpha - 1}}{\frac{1}{\alpha(p' + 1)} e^{-\omega Z} + \frac{\alpha p'}{\alpha - 1}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4.7)$$

In the denominators of the expressions for q, q', the term involving $e^{-\omega Z}$ is generally small and the difference between these two terms negligible. We are thus led to the relation

$$1 < q'/q < 1 + (\alpha - 1)(\lambda/l) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4.8)$$

It follows from (4.8) that for all moderate values of λ/l, q' may be taken as an adequate approximation to q. Now the expression (4.7) for q' is simply (1.9) with L, l, replaced by $L + \lambda$, $l + \lambda$ respectively. Hence if we know the value of λ we can still use the methods of Sections II and III to determine α, kZ.

V. *The Value of* α *for the* $H_2{}^{16}O$–$H_2{}^{18}O$ *System.*—The unit process separation factor for the system $H_2{}^{16}O/H_2{}^{18}O$ was first determined by Wahl and Urey (*J. Chem. Phys.*, 1935, **3**, 411) using simple evaporation of water, and analysing the increase in ^{18}O content of the residue. A similar method was used by Riesenfeld and Chang (*Z. physikal. Chem.*, 1936, **33**, 127). Using packed fractionating columns operating with a liquid feed of normal water and with small boiler, we carried out a series of production experiments. The various runs differed in conditions of production rate, flow, and pressure. The results of some of the runs are shown in the Table.

It should be emphasized that there is necessarily a pressure difference ΔP between the top of the column and its foot and so α is not constant over the length of the column. It follows that our equations and their solutions involve the use of an average value of α as an approximation. However for the small pressure differences with which we operated

the variation of α along the column is slight and it is certainly adequate to define its derived value as that for the mean pressure in the column. The values of q reported in the Table are the averages for a period at least 11 days after the steady state had been reached.

Data for the production of $H_2^{18}O$ *by fractionation of water.*

Mean pressure, mm. Hg	ΔP, mm. Hg	L, l./day	p	$q_{obs.}$	$q_{calc.}$
Column A.					
257	75	51·7	0·00290	3·22	3·26
259	78	50·1	0·00200	4·10	4·10
271	52	37·9	0·000849	8·26	8·18
274	48	36·7	0·000540	11·23	11·30
265	42	33·3	0·000593	11·20	11·24
Column B.					
355	130	57·5	0·00348	3·08	3·08
355	130	57·5	0·00174	5·05	5·04
355	130	57·5	0·00087	8·52	8·49
355	130	57·5	0·00261	3·74	3·75

Column A (Rehovoth, Israel) had a packed section of 90 mm. × 7 m.
Column B (London, England) had a packed section of 75 mm. × 15 m.

Great care has to be taken to ensure that q is actually the steady-state value, and to continue the production long enough for this to be beyond doubt. Otherwise transient effects arising from the initiation of production can seriously affect the value of q obtained. This error was encountered by us in earlier work before its nature was sufficiently appreciated. A physical explanation and theoretical discussion will be given in a subsequent paper of this series.

It was assumed that λ/l was constant for each column. This assumption, although inexact, is probably sufficiently accurate for practical purposes. In both columns A and B the water was fed at room temperature and it can be calculated that this would lead to a condensation of vapour equivalent to 10% of the inflow. This amount is the lower limit for λ/l and in practice a slightly higher value may be expected as a result of heat losses in the upper parts of the columns. For each column the values of λ/l, α, kZ were determined by a "least squares" method. The data of column A led to $\alpha = 1{\cdot}0065$, $kZ = 22{,}940$, $\lambda/l = 0{\cdot}10$. Column B gave $\alpha = 1{\cdot}0064$, $kZ = 40{,}200$, $\lambda/l = 0{\cdot}15$. The values of q calculated with these values of the constants are shown in the last column of the Table.

It should be remarked that the slightly lower value of α for column B may be associated with the higher pressure of operation compared with column A. Also the higher value of λ/l is readily understood if we take into account the fact that the London environment was on the average much colder than that at Rehovoth and, moreover, that column B was provided with a steam jacket to compensate for heat loss from its walls. It is interesting also to note that $(kZ)_B/(kZ)_A = 1{\cdot}75$ though $Z_B/Z_A = 2{\cdot}14$. This is in accordance with the known physical fact that the "number of theoretical plates" does not increase proportionally with an increase in the length of the column.

The satisfactory agreement between the observed and the calculated values of q confirms the validity of the model described by the differential equations and, incidentally, the inverse proportion between L and the number of theoretical plates.

The value of α which we have derived for the $H_2^{16}O$–$H_2^{18}O$ system is seen to be in substantial agreement with that obtained by Wahl and Urey (*loc. cit.*) ($\alpha = 1{\cdot}0066$ at 300 mm.), but somewhat higher than that given by Riesenfeld and Chang (*loc. cit.*) ($\alpha = 1{\cdot}0052$ at 300 mm.).

VI. *The Value of* α *for the* H_2O–HDO *System.*—For this system, with its comparatively high value of α and correspondingly low value of $\exp\{(-kZ/L) \cdot (\alpha - 1)\}$, the enrichment is determined by the rate of production and depends hardly at all on the length of our column. This is equivalent to saying that our column is effectively infinite for the system and so q is given quite simply by (2.1), but using p' instead of p (cf. equation 4.6). The enrichment of deuterium was measured for the last two runs of column A reported in the Table. The values were 78 ± 4 and 70 ± 5 respectively. Applying the modified

equation (2.1) and using $\lambda/l = 0{\cdot}1$ we obtain for α the respective values $1{\cdot}038 \pm 0{\cdot}003$, $1{\cdot}038 \pm 0{\cdot}002$. This result is in agreement with the values given by Riesenfeld and Chang (*op. cit.*) for the pressures used.

We remark that the column was designed and operated for the production of $H_2{}^{18}O$ and in consequence the conditions with respect to HDO production were far from optimal and could be regarded as wasteful.

In conclusion the authors express their appreciation to Drs. C. A. Bunton and F. Klein for the numerous mass-spectrometric analyses performed, and to Professor E. D. Hughes, F.R.S., for his continued interest in this work. One of the authors (D. R. Llewellyn) acknowledges with gratitude the tenure of an I.C.I. Fellowship at University College, London.

Appendix

Tables of Γ *functions for various values of* q.

$q = 3$		$q = 4$		$q = 5$		$q = 6$	
X	*Y*	*X*	*Y*	*X*	*Y*	*X*	*Y*
0·305	0·590	0·48	0·682	0·605	0·723	0·700	0·813
0·310	0·525	0·485	0·609	0·61	0·655	0·710	0·661
0·33	0·418	0·49	0·568	0·62	0·590	0·720	0·609
0·35	0·363	0·50	0·520	0·63	0·550	0·730	0·576
0·37	0·325	0·51	0·486	0·64	0·522	0·740	0·551
0·39	0·296	0·52	0·460	0·65	0·500	0·75	0·530
0·42	0·263	0·54	0·420	0·66	0·481	0·76	0·513
0·44	0·245	0·56	0·391	0·68	0·451	0·77	0·498
0·46	0·229	0·58	0·367	0·70	0·427	0·79	0·474
0·50	0·203	0·60	0·348	0·72	0·408	0·80	0·463
0·55	0·177	0·64	0·316	0·76	0·377	0·82	0·445
0·60	0·157	0·68	0·293	0·80	0·354	0·84	0·429
0·65	0·140	0·725	0·271	0·84	0·335	0·86	0·415
0·70	0·127	0·775	0·252	0·86	0·326	0·90	0·393
0·75	0·116	0·85	0·230	0·90	0·312	0·95	0·371
0·80	0·106	0·90	0·218	0·95	0·297	1·00	0·354
0·90	0·091	1·00	0·200	1·00	0·285	1·1	0·328
1·00	0·080	1·1	0·186	1·1	0·266	1·2	0·310
1·25	0·062	1·3	0·169	1·2	0·252	1·3	0·297
1·50	0·052	1·5	0·158	1·3	0·242	1·5	0·280
1·75	0·047	1·7	0·152	1·5	0·228	1·8	0·266
2·00	0·045	2·0	0·147	1·75	0·219	2·25	0·258
3·40	0·041	2·5	0·144	2·0	0·213	2·5	0·256
4·00	0·041	3·0	0·142	3·0	0·207	3·0	0·254

$q = 7$		$q = 8$		$q = 9$		$q = 10$	
X	*Y*	*X*	*Y*	*X*	*Y*	*X*	*Y*
0·78	0·806	0·85	0·762	0·905	0·838	0·955	0·888
0·785	0·721	0·855	0·711	0·91	0·751	0·96	0·774
0·79	0·680	0·86	0·681	0·915	0·714	0·965	0·735
0·80	0·632	0·87	0·641	0·92	0·688	0·97	0·708
0·81	0·600	0·88	0·613	0·925	0·669	0·975	0·686
0·82	0·576	0·89	0·591	0·93	0·652	0·98	0·670
0·83	0·556	0·90	0·573	0·94	0·625	0·99	0·646
0·84	0·540	0·92	0·544	0·95	0·605	1·00	0·622
0·85	0·526	0·94	0·522	0·96	0·587	1·02	0·590
0·86	0·513	0·96	0·504	0·98	0·560	1·04	0·567
0·87	0·502	0·98	0·488	1·00	0·539	1·06	0·550
0·88	0·491	1·00	0·475	1·25	0·517	1·1	0·518
0·89	0·482	1·1	0·428	1·05	0·500	1·2	0·471
0·925	0·456	1·2	0·399	1·75	0·485	1·3	0·442
0·95	0·440	1·3	0·379	1·1	0·473	1·4	0·422
1·0	0·415	1·4	0·364	1·2	0·436	1·5	0·408
1·1	0·381	1·5	0·354	1·3	0·412	1·6	0·397
1·2	0·358	1·6	0·346	1·4	0·395	1·7	0·386
1·3	0·341	1·7	0·340	1·5	0·382	1·8	0·383
1·5	0·320	1·8	0·335	1·6	0·373	1·9	0·379
1·7	0·308	1·9	0·331	1·8	0·361	2·0	0·375
2·0	0·298	2·0	0·329	2·0	0·354	2·2	0·370
2·5	0·292	2·5	0·321	2·5	0·346	2·6	0·366
3·0	0·290	3·0	0·319	3·0	0·343	3·0	0·363

APPENDIX—*continued.*

$q = 11$		$q = 12$		$q = 15$		$q = 20$	
X	Y	X	Y	X	Y	X	Y
1·005	0·796	1·045	0·825	1·15	0·841	1·285	0·838
1·01	0·753	1·05	0·770	1·155	0·791	1·29	0·802
1·015	0·722	1·06	0·716	1·16	0·761	1·295	0·778
1·02	0·701	1·07	0·684	1·165	0·740	1·30	0·760
1·025	0·684	1·075	0·671	1·17	0·723	1·31	0·732
1·03	0·669	1·08	0·660	1·175	0·708	1·32	0·712
1·04	0·646	1·09	0·641	1·18	0·696	1·34	0·682
1·05	0·627	1·10	0·625	1·19	0·676	1·35	0·670
1·06	0·612	1·125	0·600	1·20	0·660	1·375	0·646
1·08	0·587	1·15	0·572	1·22	0·634	1·4	0·627
1·1	0·567	1·175	0·553	1·24	0·614	1·425	0·612
1·12	0·550	1·2	0·538	1·26	0·600	1·45	0·560
1·14	0·536	1·25	0·514	1·28	0·584	1·475	0·589
1·16	0·524	1·3	0·495	1·35	0·548	1·5	0·579
1·18	0·514	1·35	0·481	1·4	0·530	1·55	0·563
1·2	0·504	1·4	0·469	1·45	0·516	1·6	0·551
1·25	0·485	1·5	0·451	1·5	0·504	1·65	0·541
1·3	0·469	1·6	0·439	1·6	0·486	1·7	0·532
1·4	0·446	1·7	0·428	1·7	0·474	1·8	0·519
1·5	0·430	1·8	0·421	1·8	0·464	1·9	0·509
1·7	0·410	2·0	0·411	2·0	0·452	2·0	0·502
2·0	0·394	2·2	0·405	2·2	0·445	2·2	0·492
2·4	0·385	2·6	0·399	2·6	0·437	2·6	0·483
3·0	0·381	3·0	0·397	3·0	0·434	3·0	0·479

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674. *Synthetic Analgesics and Related Compounds. Part V.* 2-Imino-3 : 3-diphenylpyrrolidines.*

By WALTER WILSON.

Several γ-benzylmethylamino-cyanides of the amidone series are converted smoothly in boiling hydrochloric acid into 2-iminopyrrolidines and benzyl chloride. The mechanism of the reaction is discussed and also the conversion of the products by nitrous acid into pyrrolid-2-ones. The latter characterise the original 2-iminopyrrolidines.

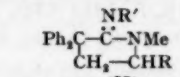
IN Part I (*J.*, 1950, 2173) the 2-iminopyrrolidine structure (II; R = Me, R′ = H) was proposed for a base (m. p. 103°) obtained by heating 3-dimethylamino-1 : 1-diphenylbutyl cyanide (I; R = Me) with ethylenediamine (both as arylsulphonates). It has been reported that 2-iminopyrrolidines are formed by heating salts of γ-dialkylamino-cyanides of the amidone series (Blicke and Zambito, Abs. 111th Meeting Amer. Chem. Soc., 1947, 3K; Blicke, U.S.P., 2,513,279; *Chem. Abs.*, 1951, **45**, 5187). Some possible alternative routes to 2-iminopyrrolidines have now been examined.

The cyanide (III; R = Ph) was readily obtained by condensing 2-methylanilinoethyl chloride with diphenylmethyl cyanide. Attempts to remove the *N*-phenyl group by nitrosation and digestion with alkali failed. The acids (IV; R = H and R = Me) were produced in good yields from methyl acrylate and 1-methacrylate, respectively, and diphenylmethyl cyanide in sodium ethoxide; (IV; R = H) has been obtained previously by a less convenient method using ethyl 3-bromopropionate (Trivedi *et al.*, *J. Univ. Bombay*, **1942**, **10**, 135). The amide of (IV; R = H) gave an anomalous product under the conditions of the Hofmann reaction; similarly an anomalous product was obtained from the hydrazide of (IV; R = Me) by the Curtius reaction.

* Part IV, *J.*, 1952, 1321.

The γ-benzylmethylamino-cyanide (III; R = CH_2Ph) was converted smoothly into benzyl chloride and the 2-iminopyrrolidine (II; R = R′ = H) (hydrochloride, m. p. 223·5—224°) in boiling hydrochloric acid. The structure of the product was confirmed by the formation of the known pyrrolid-2-one (VII; R = H) with nitrous acid. The unidentified hydrochloride, m. p. 226—228°, obtained by Morrison and Rinderknecht (*J.*, 1950, 1478) by hydrogenating the hydrochloride of the cyanide (III; R = $CHPh_2$) was probably an impure (hydrated?) form of the same 2-iminopyrrolidine hydrochloride.

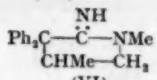
$Ph_2C(CN)\cdot CH_2\cdot CHMe\cdot NMeR$ (I)


(II)

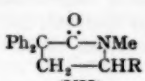
$Ph_2C(CN)\cdot CH_2\cdot CH_2\cdot NMeR$ (III)

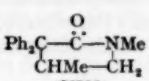
$Ph_2C(CN)\cdot CH_2\cdot CHR\cdot CO_2H$ (IV)

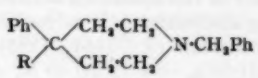
$Ph_2C(CN)\cdot CHMe\cdot CH_2\cdot NMe\cdot CH_2Ph$ (V)


(VI)

Two isomeric basic cyanides (I; R = CH_2Ph) and (V) were obtained by treating diphenylmethyl cyanide with *N*-benzyl-2-chloro-*N*-methylpropylamine; formation of two isomers in similar reactions has been observed previously (*e.g.*, Bockmuhl and Ehrhart, *Annalen*, 1948, **561**, 52; Schultz, Robb, and Sprague, *J. Amer. Chem. Soc.*, 1947, **69**, 2454; Ofner, *J.*, 1951, 1800). Both basic cyanides were smoothly debenzylated in boiling hydrochloric acid. The resulting 2-iminopyrrolidines (II; R = Me, R′ = H) and (VI) were isolated as the hydrochlorides, which gave the known pyrrolid-2-ones (VII; R = Me)


(VII)

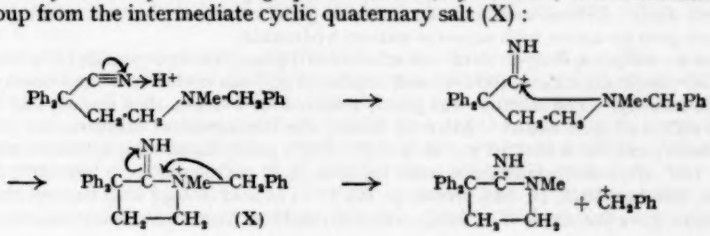

(VIII)


(IX)

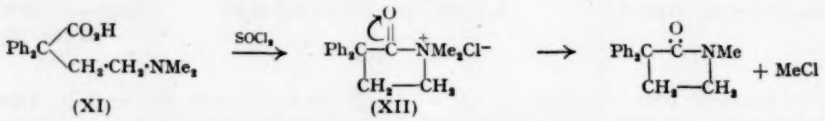
and (VIII) respectively, with nitrous acid. The structures of the two iminopyrrolidines and of the original basic cyanides are therefore established. Cymerman and Gilbert (*J.*, 1952, 3529) has obtained (II; R = Me, R′ = H) from 3-dimethylamino-1 : 1-diphenylbutyl cyanide (I; R = Me) and ammonium benzenesulphonate at 260°; specimens of the base and hydrochloride provided by Dr. Cymerman were identical with the materials obtained here. The compound (m. p. 103°), for which the structure (II; R = Me, R′ = H) was proposed in Part I, is different, and is being examined further. The 2-iminopyrrolidine (II; R = Me, R′ = H) gave an *N*-acetyl derivative, which was *soluble* in dilute acid. This provides independent confirmation of the structure, as the compound (II; R = Me, R′ = Ac) could be basic, but the open-chain isomer (I; R = Ac) would be neutral.

The effective reagent in the debenzylating ring closures described is probably the water–hydrogen chloride azeotrope at the boiling point (108·6°/760 mm.; 20·2% HCl by wt.). These conditions are much milder than those customary for the pyrolytic debenzylation of simple tertiary benzylammonium chlorides (*e.g.*, Collie and Schryver, *J.*, 1890, 781, used temperatures of >300°).

It is believed that 2-iminopyrrolidines and benzyl chloride are formed from γ-benzylmethylamino-cyanides by a two-stage process: first, cyclisation, then elimination of the benzyl group from the intermediate cyclic quaternary salt (X):



The first stage is analogous to the well-known formation of amidines from cyanides and amine salts (Oxley and Short, *J.*, 1946, 147, and later papers), whilst the removal of the benzyl cation from (X) would be facilitated by the electromeric displacement $\rangle C{=}\overset{\curvearrowright}{N}H$. The preferential elimination of benzyl instead of methyl would be expected, as in the simpler cases discussed by Hanhart and Ingold (*J.*, 1927, 1002). Attempts to make the chlorides of acids such as (XI) often yield pyrrolidones (Clarke, Mooradian, Lucas, and Slauson, *J. Amer. Chem. Soc.*, 1949, **71**, 2821; Dupré, Elks, Hems, Speyer, and Evans, *J.*, 1949, 502; Walton, Ofner, and Thorp, *J.*, 1949, 649). In this reaction, it is probable that an intermediate is the cyclic quaternary salt (XII). Elimination of an alkyl group would be facilitated by the $\rangle C{=}\overset{\curvearrowright}{O}$ displacement, and thus there is a close resemblance to the proposed mechanism of iminopyrrolidine formation :



(XI) (XII)

It would be sterically difficult for the *N*-benzylpiperidyl cyanide (IX; R = CN) to form a cyclic quaternary salt analogous to (X). Indeed, this cyanide was not debenzylated under the usual conditions, but was converted slowly into the corresponding carboxylic acid (IX; R = CO_2H).

The formation of pyrrolid-2-ones from 2-iminopyrrolidines and nitrous acid is difficult to explain in the examples studied because imino-amino-tautomerism is impossible. The following mechanism seems feasible, and recalls the scheme proposed by Barrott, Gillibrand, and Lamberton (*J.*, 1951, 1285) for the alkali-catalysed decomposition of nitramines ($\rangle CH{\cdot}NH{\cdot}NO_2 \longrightarrow \rangle C{:}O + N_2 + H_2O$) :

$$\rangle C{=}NH \xrightarrow{HNO_2} \rangle C{=}\overset{\curvearrowright}{N}{-}N{=}\overset{\curvearrowright}{O} \xrightarrow{H^+} \rangle \overset{+}{C}{-}N{=}N{-}OH \xrightarrow{OH} \rangle C(OH){\cdot}N{:}N{\cdot}OH \longrightarrow \rangle C{:}O + N_2 + H_2O$$

Experimental

2-Methylanilinoethyl Chloride.—Methylaniline (160·5 g.) and ethylene chlorohydrin (80·5 g.) were heated at 100° under reflux (Laun, *Ber.*, 1884, **17**, 676, used a sealed tube) for 35 hours. Distillation gave 2-methylanilinoethanol (198 g., 88%), b. p. 150°/14 mm., which with phosphorus oxychloride in benzene (Anker and Cook, *J.*, 1944, 490) gave 2-methylanilinoethyl chloride (40%), b. p. 124—127°/19 mm. The latter became intensely blue when kept, and formed a *picrate*, m. p. 108—109·5°, bright yellow prisms from ethanol (Found: C, 45·3; H, 3·85. $C_9H_{12}NCl,C_6H_3O_7N_3$ requires C, 45·1; H, 3·75%).

3-Methylanilino-1 : 1-diphenylpropyl Cyanide.—Diphenylmethyl cyanide (19·3 g.) in benzene (60 c.c.) was stirred with powdered sodamide (4·7 g.) for 30 minutes at 40°. 2-Methylanilinoethyl chloride (17 g.) in benzene (20 c.c.) was added and the mixture heated at 70—80° for 6 hours. The benzene solution was washed with water then with 3N-hydrochloric acid. The aqueous acid extract was basified, which caused precipitation of 2-methylanilinoethyl chloride (3·6 g.), b. p. 122—126°/18 mm., identified as the picrate. Evaporation of the benzene solution and recrystallisation of the residue from ethanol gave *3-methylanilino-1 : 1-diphenylpropyl cyanide* (25 g.) as white needles, m. p. 143·5—144° (Found: C, 85·05, 85·3; H, 6·5, 6·9; N, 9·1. $C_{23}H_{22}N_2$ requires C, 84·7; H, 6·75; N, 8·6%). The compound was almost insoluble in dilute hydrochloric acid. Nitrous acid gave an unstable green nitroso-derivative, which polymerised rapidly, and gave no amine with aqueous sodium hydroxide.

4-Cyano-4 : 4-diphenylbutyric Acid.—A solution of diphenylmethyl cyanide (50 g.) in ethanolic sodium ethoxide [from ethanol (60 c.c.) and sodium (6 g.)] was cooled to 0° and methyl acrylate (30 g.) added slowly. The mixture was gently refluxed for 2 hours, then cooled, and 5N-sodium hydroxide (125 c.c.) was added. After 36 hours, the homogeneous mixture was poured into excess of water, and the acid (39·2 g.; m. p. 157—160°) precipitated with hydrochloric acid. It had m. p. 160° after recrystallisation from benzene–light petroleum (b. p. 40—60°) (Trivedi *et al.*, *J. Univ. Bombay*, 1942, **10**, 135, give m. p. 160°). The acid (8·5 g.) with thionyl chloride and then ammonia, gave the *amide* (7 g., 83%), which crystallised from aqueous methanol in glistening

flakes, m. p. 129° (Found : N, 10·85. $C_{17}H_{16}ON_2$ requires N, 10·6%); treatment with bromine and sodium methoxide did not give the expected basic product.

γ-Cyano-α-methyl-γ : γ-diphenylbutyric Acid.—In a condensation similar to the preceding, methyl 1-methylacrylate gave, after recrystallisation of the crude solid from benzene–light petroleum (b. p. 100—120°), the homologous *acid* (89%), m. p. 140·5° (Found : C, 77·45; H, 6·05. $C_{18}H_{17}O_2N$ requires C, 77·5; H, 6·1%). The acid (10 g.) in ethanol (50 c.c.) was mixed with acetyl chloride (2 c.c.), left for 18 hours, then refluxed for 30 minutes. Evaporation gave the *ethyl* ester (8·6 g., 78%), which formed small prisms, m. p. 110°, from benzene–light petroleum (Found : N, 4·6. $C_{20}H_{21}O_2N$ requires N, 4·55%). The ester (1·0 g.) with aqueous-alcoholic 2N-sodium hydroxide (25 c.c.) at 20° for 48 hours gave the original acid (0·85 g.), m. p. 140°. The ester (3·1 g.), when heated under reflux for 8 hours with 90% hydrazine hydrate (4·5 c.c.) in ethanol (10 c.c.), gave the *hydrazide* (2·55 g., 86%), which crystallised from ethanol as glistening prisms, m. p. 195—196° (Found : N, 14·05. $C_{18}H_{19}ON_3$ requires N, 14·35%). Heating the hydrazide (100 mg.) with benzaldehyde (100 mg.) in ethanol (5 c.c.) for 1½ hours gave the *benzylidenehydrazide* (110 mg.), which formed pale yellow prisms, m. p. 199·5—200°, from ethanol (Found : N, 11·05. $C_{25}H_{23}ON_3$ requires N, 11·0%). A normal Curtius reaction did not occur when the hydrazide was treated with nitrous acid; the product was soluble in alkali.

2-*Benzylaminoethanol.*—A modification of the method of Rumpf and Kwass (*Bull. Soc. chim.*, 1943, **10**, 349) was used. A mixture of 2-hydroxyethylamine (61 g.) and benzyl chloride (63·3 g.) was set aside for 2 weeks, then heated to 100° for 6 hours. Excess of sodium hydroxide solution was added and the oily upper layer distilled, giving 2-benzylaminoethanol (33 g., 44%), b. p. 153—156°/12 mm., and 2-dibenzylaminoethanol (15 g., 25%), b. p. 195—205°/16 mm. (yields are calculated on benzyl chloride).

2-*Benzylmethylaminoethanol.*—(a) From 2-*benzylaminoethanol*. The amino-alcohol (27 g.), paraformaldehyde (5·4 g.), and formic acid (30 c.c.; *d* 1·2) were heated together at 70—80°, and, when the vigorous reaction subsided, refluxed for 4 hours. The liquid was evaporated to small bulk at 100°/15 mm., and excess of sodium hydroxide added. The base (25 g., 85%), isolated by extraction with ether–benzene, had b. p. 132—133°/12 mm., n_D^{22} 1·5225.

(b) *From benzylmethylamine*. A mixture of benzylmethylamine (24·2 g.) and ethylene chlorohydrin (16·1 g.) was set aside for 3 days, then heated at 100° for 7 hours. Isolation as in (*a*) gave 2-benzylmethylaminoethanol (17 g., 51%), b. p. 129—132°/12 mm., n_D^{22} 1·5270 (cf. Mannich and Kuphal, *Arch. Pharm.*, 1912, **250**, 542, who used a sealed tube for the reaction, and Ofner and Walton, *J.*, 1950, 2166, who used ethylene oxide instead of chlorohydrin).

2-*Benzylmethylaminoethyl Chloride.*—2-Benzylmethylaminoethanol (41 g.) was converted into the crude chloroamine hydrochloride (Sheehan and Mumaw, *J. Amer. Chem. Soc.*, 1950, **72**, 2129; Ofner and Walton, *J.*, 1950, 2165). The crude salt was dissolved in water and filtered through kieselguhr, and 10N-sodium hydroxide (30 c.c.) was added. The chloro-amine (36 g., 79%), b. p. 120°/16 mm., n_D^{18} 1·5238, was isolated by ether. The *picrate* formed needles, m. p. 103—104°, from ethanol (Found : N, 13·65. $C_{10}H_{14}NCl,C_6H_3O_7N_3$ requires N, 13·6%).

3-*Benzylmethylamino*-1 : 1-*diphenylpropyl Cyanide.*—Reaction between 2-benzylmethylaminoethyl chloride, diphenylmethyl cyanide, and sodamide (Walton and Ofner, *J.*, 1950, 2165) gave the cyanide, b. p. 205—212°/0·2 mm., in 81% yield. The hydrochloride was a water-insoluble syrup, and the *picrate* formed glistening flakes, m. p. 161—162°, from ethanol (Found : N, 13·2. $C_{24}H_{44}N_2,C_6H_3O_7N_3$ requires N, 12·3%).

1-*Benzylaminopropan*-2-*ol.*—Propylene oxide (58 g.) was stirred for 24 hours with benzylamine (107 g.) and water (100 c.c.), with cooling when necessary to keep the temperature below 60°. Distillation yielded benzylamine, b. p. 95—100°/11 mm. (16 g., 15%), 1-benzylaminopropan-2-ol, b. p. 145—150°/11 mm. (74 g., 45%), and benzyldi-(2-hydroxypropyl)amine, b. p. 175—195°/11 mm. (60·5 g., 25%) (yields calc. on benzylamine). 1-Benzylaminopropan-2-ol has been made previously by other methods (Uedinck, *Ber.*, 1899, **32**, 969; Staub, *Helv. Chim. Acta*, 1922, **5**, 891).

1-*Benzylmethylaminopropan*-2-*ol.*—(a) *From* 1-*benzylaminopropan*-2-*ol*. The amino-alcohol (74 g.) was heated under reflux for 20 hours with paraformaldehyde (13·5 g.), water (60 c.c.), and formic acid (20 c.c.; *d* 1·2). More formic acid (60 c.c.) was added, and refluxing continued for 8 hours. Volatile substances were distilled off at 15 mm. and the residue made strongly alkaline with sodium hydroxide solution. The oily layer was removed and distilled, giving 1-*benzylmethylaminopropan*-2-*ol* (65 g., 81%), b. p. 129°/12 mm., n_D^{20} 1·5038 (Found : C, 71·8; H, 9·3. $C_{11}H_{17}ON$ requires C, 73·8; H, 9·5%). The *picrate* crystallised from ether–ethyl acetate as prisms, m. p. 80—80·5° (Found : C, 50·2; H, 5·1. $C_{11}H_{17}ON,C_6H_3O_7N_3$ requires C, 50·0; H, 4·9%).

(b) *From benzylmethylamine.* Propylene oxide (29 g.) was stirred for 20 hours with benzylmethylamine (60·5 g.) and water (50 c.c.), with intermittent cooling to keep the temperature below 50°. Fractionation of the product (two liquid phases) yielded the amino-alcohol (72 g., 88%), b. p. 122°/8 mm.

N-Benzyl-2-chloro-N-methylpropylamine.—The above amino-alcohol (61·7 g.) was converted into the crude dry hydrochloride, which was heated for 3 hours with thionyl chloride (50 c.c.) in chloroform (50 c.c.). Volatile compounds were distilled off under reduced pressure and the residue digested with acetone (100 c.c.), which gave a solid (57·4 g.), m. p. 164—167°. A small portion, recrystallised from ethanol–acetone, gave the pure *hydrochloride* as prisms, m. p. 166—167° (Found: C, 56·3; H, 7·0. $C_{11}H_{16}NCl$,HCl requires C, 56·4; H, 7·3%). The crude hydrochloride was converted as before into the *chloro-amine* (33 g., 48%), b. p. 130—132°/20 mm., n_D^{20} 1·5072 (Found: C, 66·55; H, 7·8. $C_{11}H_{16}NCl$ requires C, 66·9; H, 8·1%). The *picrate* crystallised from ethanol as flakes, m. p. 145° (Found: C, 47·55; H, 4·75. $C_{11}H_{16}NCl$ $C_6H_3O_7N_3$ requires C, 47·8; H, 4·45%).

Reaction of N-Benzyl-2-chloro-N-methylpropylamine with Diphenylmethyl Cyanide.—The cyanide (30 g.), dry benzene (100 c.c.), and powdered sodamide (7·3 g.) were stirred at 30—40° for 30 minutes. The chloro-amine (30·6 g.) in benzene (30 c.c.) was added and the mixture refluxed for 2½ hours. The benzene solution was washed with water, and most of the benzene distilled off. Light petroleum (b. p. 60—80°) was added and the crystals (9 g.), m. p. 99—102°, which slowly formed were isolated and recrystallised from benzene–light petroleum (b. p. 40—60°), giving, as white needles, m. p. 106·5—107·5°, *3-benzylmethylamino-2-methyl-1 : 1-diphenylpropyl cyanide* (Found: C, 84·5; H, 7·25; N, 7·8. $C_{25}H_{26}N_2$ requires C, 84·7; H, 7·35; N, 7·9%). This base gave a viscous, oily hydrochloride, insoluble in water but soluble in alcohols. The liquors from which the base had crystallised were evaporated and treated with methanolic hydrogen chloride; a fibrous white solid (13 g.; m. p. 194—198°) was slowly deposited. Recrystallisation from ethanol–ether–acetone gave as a white microcrystalline solid, m. p. 206°, *3-benzylmethylamino-1 : 1-diphenylbutyl cyanide hydrochloride* (Found: C, 76·4; H, 6·95. $C_{25}H_{26}N_2$,HCl requires C, 77·0; H, 6·9%). The free base was an oil. No attempt was made to find the optimum conditions for separating the isomers.

Conversion of γ-Benzylmethylamino-cyanides into 2-Iminopyrrolidines.—(*a*) 3-Benzylmethylamino-1 : 1-diphenylpropyl cyanide (3·4 g.) and concentrated hydrochloric acid (40 c.c.) were vigorously refluxed for 48 hours. Steam-distillation and extraction of the distillate with ether afforded benzyl chloride (0·65 g.), characterised by conversion into *S*-benzylthiuronium picrate, m. p. 183—185°. The solution of non-volatile substances was evaporated to dryness and the resulting *2-imino-1-methyl-3 : 3-diphenylpyrrolidine hydrochloride* (2·5 g.) recrystallised from ethanol–ether; it formed white needles, m. p. 223·5—224°, which lost solvent of crystallisation and gave a hygroscopic powder on drying at 140°/12 mm. for analysis (Found: C, 70·75; H, 6·6. $C_{17}H_{18}N_2$,HCl requires C, 71·3; H, 6·65%). The free base was an oil, and the picrate was a syrup, readily soluble in ether. The hydrochloride was dissolved in warm dilute hydrochloric acid, and sodium nitrite added. The resulting neutral solid, recrystallised from aqueous methanol, gave 1-methyl-3 : 3-diphenylpyrrolid-2-one as prisms, m. p. 144° (Dupré, Elks, Hems, Speyer, and Evans, *J.*, 1949, 507, give m. p. 146·5—147°).

(*b*) 2-Benzylmethylamino-2-methyl-1 : 1-diphenylpropyl cyanide (1·7 g.) and concentrated hydrochloric acid (20 c.c.) were refluxed for 8 hours, to give benzyl chloride (0·3 g.) and *2-imino-1 : 4-dimethyl-3 : 3-diphenylpyrrolidine hydrochloride* (1·4 g.), solvated prisms, m. p. 239°, from *iso*propyl alcohol–ether; the crystals, after being dried at 140°/12 mm. for analysis, were hygroscopic (Found: C, 72·3; H, 6·8; N, 9·1. $C_{18}H_{20}N_2$,HCl requires C, 71·9; H, 7·6; N, 9·3%). Hot dilute hydrochloric acid and sodium nitrite gave quantitatively 1 : 4-dimethyl-3 : 3-diphenylpyrrolidone, which formed glistening flakes, m. p. 122° (Walton, Ofner, and Thorp, *J.*, 1949, 654, give m. p. 121—123°); the m. p. of a mixture with the isomeric pyrrolidone from (*c*) was much lower.

(*c*) 3-Benzylmethylamino-1 : 1-diphenylbutyl cyanide hydrochloride (2 g.) and concentrated hydrochloric acid (30 c.c.) refluxed for 5½ hours similarly gave benzyl chloride (0·35 g.) and *2-imino-1 : 5-dimethyl-3 : 3-diphenylpyrrolidine hydrochloride* (1·6 g.) as small cubes, m. p. 277°, from ether–*iso*propyl alcohol (Found: C, 71·9; H, 6·6; N, 9·0. $C_{18}H_{20}N_2$,HCl requires C, 71·9; H, 6·7; N, 9·3%). The *base* formed large transparent prisms, m. p. 94°, from light petroleum (b. p. 60—80°) (Found: C, 81·45; H, 7·6; N, 10·75. $C_{18}H_{20}N_2$ requires C, 81·9; H, 7·6; N, 10·6%). The base was identical (m. p. and mixed m. p.) with a specimen made by Cymerman (*loc. cit.*) by another route, but was not identical with the compound, m. p. 103°, described in Part I. The hydrochloride (0·5 g.) was warmed with acetic anhydride (0·5 c.c.) in pyridine (5 c.c.)

at 30° for 4 hours. The pyridine was distilled off, and the residue made alkaline and extracted with benzene. The syrup obtained by evaporating the benzene, when triturated with light petroleum (b. p. 60—80°), gave a solid (0·18 g.), m. p. 123—125°. Recrystallisation from benzene–light petroleum afforded 2-*acetimido*-1 : 5-*dimethyl*-3 : 3-*diphenylpyrrolidine* as stout opaque rods, m. p. 126·5—127·5° (Found : C, 78·15; H, 7·1. $C_{20}H_{22}ON_2$ requires C, 78·45; H, 7·2%). This acetyl compound was soluble in 2N-hydrochloric acid. The 2-iminopyrrolidine hydrochloride, with hot dilute hydrochloric acid and sodium nitrite, gave quantitatively 1 : 5-dimethyl-3 : 3-diphenylpyrrolid-2-one, m. p. 119·5—120°, m. p. undepressed on admixture with an authentic specimen made by Gardner, Easton, and Stevens's method (*J. Amer. Chem. Soc.*, 1948, **70**, 2906; cf. Walton, Ofner, and Thorp, *J.*, 1949, 653).

Action of Concentrated Hydrochloric Acid on 1-*Benzyl*-4-*phenylpiperid*-4-*yl Cyanide*.—The base (5·3 g.; Part I, p. 2174) and concentrated hydrochloric acid (25 c.c.) were refluxed for 34 hours; no benzyl chloride was formed. The acid was distilled off and the residue treated with excess of sodium hydroxide solution. Unchanged base (1·07 g.; m. p. 69—71°) was filtered off; the filtrate was neutralised with acetic acid, which precipitated 1-benzyl-4-phenylpiperidine-4-carboxylic acid (2·3 g.), which decomposed rapidly above 265° [Eisleb, *Ber.*, 1941, **74**, 1433 gives m. p. 288° (decomp.)]. For identification, the acid (1·75 g.) was refluxed for 6 hours with ethanol (25 c.c.) and concentrated sulphuric acid (5 c.c.), and gave the ethyl ester (1·5 g.), m. p. 72—73° (Eisleb, *loc. cit.*, gives m. p. 73—74°).

The author is grateful to Professor M. Stacey, F.R.S., for encouragement, and thanks Mr. E. Lunt for preliminary experiments with 2 : 2-diphenylbutyric acids, Messrs. R. P. Smith and S. Nielsen for preparing 2-methylanilinoethyl chloride, and Messrs. B. Stringer and D. Skidmore for the microanalyses.

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675. *Some Reactions of* 3-*Dimethylamino*-1 : 1-*diphenylbutyl Cyanide*.

By J. CYMERMAN and W. S. GILBERT.

Reaction of 3-dimethylamino-1 : 1-diphenylbutyl cyanide (I) with ammonium benzenesulphonate has yielded 2-imino-1 : 5-dimethyl-3 : 3-diphenylpyrrolidine (II; R = Me). With a large excess of the ammonium compound (I) appears to give 2-imino-5-methyl-3 : 3-diphenylpyrrolidine (II; R = H). Ultra-violet absorption spectra of these and a number of related compounds have been determined.

THE reaction of (±)-3-dimethylamino-1 : 1-diphenylbutyl cyanide (I) with ethylenediamine at 200° for 27·5 hours was reported by Wilson (*J.*, 1950, 2173) to give a base, m. p. 103°, believed to be 2-imino-1 : 5-dimethyl-3 : 3-diphenylpyrrolidine (II; R = Me). We have now examined the reaction of (I) with ammonium benzenesulphonate. Interaction of equimolecular quantities of (I) and ammonium benzenesulphonate at 255—260° for 4 hours gave, *via* a hydrochloride (50% yield), a crystalline base. Analyses and chemical properties indicated the structure (II; R = Me) for our base; however, a mixed m. p. (carried out by Dr. Wilson) with the product (m. p. 103°) described by Wilson (*loc. cit.*) showed a large depression in m. p. We now learn (Dr. W. Wilson, personal communication) that an independent synthesis of (II; R = Me) has given a base, m. p. 93·5—94° (hydrochloride, m. p. 277°). The identity of our base and Wilson's product of m. p. 93·5—94° was confirmed by a mixed m. p. determination for which we are indebted to Dr. Wilson. Professor R. H. Thorp kindly examined this compound for analgesic activity, but it was devoid of appreciable activity.

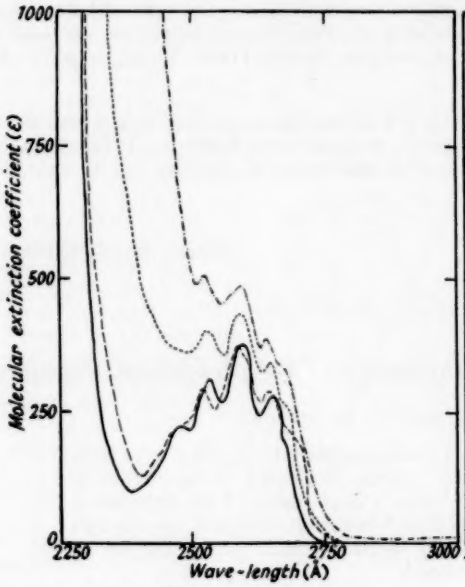
Reaction of (I) with ammonium benzenesulphonate (3 mols.) at 255—260° for 4 hours afforded, in addition to the hydrochloride of (II; R = Me), a small yield of a by-product, $C_{22}H_{22}N_2$, possessing 2 *N*-methyl groups. Its nature was not further investigated.

Treatment of (I) with 5 mols. of ammonium benzenesulphonate at 255—260° for 4 hours gave 34% of a base, $C_{17}H_{18}N_2$, m. p. 149·5—151·5°, which is believed to be 2-imino-5-methyl-3 : 3-diphenylpyrrolidine (II; R = H). It showed no evidence of unsaturation. Its formation would be accounted for by amine exchange with the large excess of ammonia present in the mixture, the intermediate (presumably 3-amino-1 : 1-diphenylbutyl cyanide) then cyclising to give (II; R = H) :

(I) $Ph_2{\cdot}C(CN){\cdot}CH_2{\cdot}CHMe{\cdot}NMe_2$ (II) $Ph_2{\cdot}C(C(=NH){\cdot}NR){\cdot}CH_2{\cdot}CHMe$

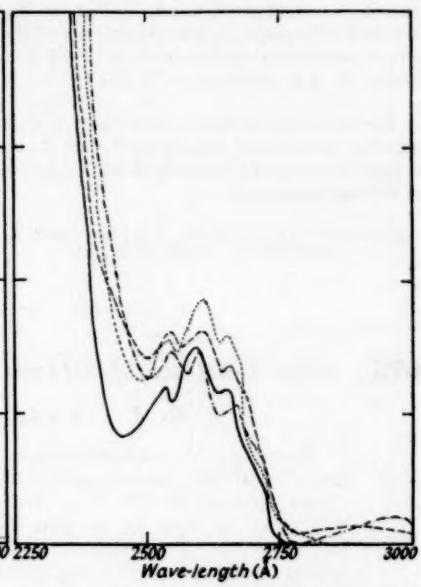
Attempted reaction of (I) with ammonia *via* the Pinner method (cf. Ashley, Barber, Ewins, Newbery, and Self, *J.*, 1942, 103) failed, no evidence of imino-ether formation being

FIG. 1.



———— *Diphenylmethyl cyanide.*
— — — — 3-*Dimethylamino*-1 : 1-*diphenylbutyl cyanide hydrochloride.*
- - - - - - - 3-*Dimethylamino*-1 : 1-*diphenylbutyl cyanide.*
— · — · — 2-*Imino*-1 : 5-*dimethyl*-3 : 3-*diphenylpyrrolidine.*

FIG. 2.



———— 2-*Imino*-1 : 5-*dimethyl*-3 : 3-*diphenylpyrrolidinium chloride.*
— — — — 6-*Dimethylamino*-4 : 4-*diphenylheptan*-3-*one.*
- - - - - - - 2-*Imino*-5-*methyl*-3 : 3-*diphenylpyrrolidine.*
— · — · — 6-*Dimethylamino*-4 : 4-*diphenylheptan*-3-*one hydrochloride.*

obtained; even after 2 weeks at 0° or after being heated at 60—65° for 6 hours, only unchanged (I) was recovered.

The ultra-violet absorption spectra of (I), (II; R = Me), and a number of related compounds in 95% alcoholic solution were determined, a Beckman quartz spectrophotometer, model DU, being used. The spectra of diphenylmethyl cyanide, of (I) and its hydrochloride, of (II; R = Me) and its hydrochloride, of (II; R = H), and of 6-dimethylamino-4 : 4-diphenylheptan-3-one (amidone) and its hydrochloride all showed similar absorption curves (Figs. 1 and 2) with intense end-absorption below 2400 Å, and three characteristic maxima at 2540, 2600, and 2650 Å with molecular extinction coefficients of about 400.

The curve obtained for amidone hydrochloride is in good agreement with that reported by Kumler, Strait, and Alpen (*J. Amer. Chem. Soc.*, 1950, **72**, 1463) but our curve for amidone does not correspond well with Ofner and Walton's absorption curve (*J.*, 1950, 2160) which shows no evidence of the characteristic fine structure in the 2600-Å region. The by-product (m. p. 212°) gave an entirely different absorption curve (see Experimental).

Experimental

2-Imino-1 : *5-dimethyl*-3 : 3-*diphenylpyrrolidine*.—A mixture of 3-dimethylamino-1 : 1-diphenylbutyl cyanide (5·6 g., 0·02 mol.) and ammonium benzenesulphonate (3·6 g., 0·02 mol.) was heated at 255—260° for 4 hours. The reaction mixture was dissolved in warm 2N-hydrochloric acid and filtered, and the cooled filtrate made alkaline with aqueous sodium hydroxide. The oily base was taken up in chloroform, and the dried (Na_2SO_4) solution treated with dry hydrogen chloride, affording on evaporation and trituration with acetone, *2-imino*-1 : *5-dimethyl*-3 : 3-*diphenylpyrrolidinium chloride* (3·0 g., 50%; m. p. 275·5—277°), crystallising from methyl cyanide–acetone in cubes, m. p. 279—281° [Found: C, 71·4, 71·8, 72·25; H, 7·15, 7·15, 7·1; N, 9·25, 9·1, 9·1; Cl, 11·15; *N*-Me, 9·45%; equiv. (by titration), 294; *M* (Niederl, Kasanov, Kisch, and Rao, *Mikrochem.*, 1949, **34**, 132), 311. $C_{18}H_{20}N_2$.HCl requires C, 71·9; H, 6·7; N, 9·3; Cl, 12·1; *N*-Me, 9·65%; equiv. and *M*, 300·5].

Vacuum distillation of the oily base obtained from the pure hydrochloride gave a viscous oil, b. p. 170°/0·9 mm., which solidified to a white solid (m. p. 90—92·5°); a mixed m. p. with (I) (m. p. 92·5°) gave m. p. 70—75°. Crystallisation from light petroleum (b. p. 60—90°) gave bipyramids of the *base*, m. p. 93—94·5° (Found: C, 81·95; H, 7·7; N, 10·25, 10·5; *N*-Me, 11·5, 12·0, 8·1. $C_{18}H_{20}N_2$ requires C, 81·9; H, 7·6; N, 10·6; *N*-Me, 11·0%); the mixed m. p. with the base of m. p. 103° (Wilson, *J.*, 1950, 2173) was 77—81°.

2-Imino-5-methyl-3 : 3-*diphenylpyrrolidine*.—A mixture of (I) (5·6 g., 0·02 mol.) and ammonium benzenesulphonate (17·5 g., 0·1 mol.) was heated at 255—260° for 4 hours. Working up of the reaction mixture as described above gave an oil which solidified on trituration with ether; the *base* (1·8 g., 34%), m. p. 129—139°, on crystallisation from aqueous alcohol, formed plates, m. p. 149·5—151·5° (Found: C, 80·95; H, 6·9; N, 10·9, 11·55. $C_{17}H_{18}N_2$ requires C, 81·55; H, 7·25; N, 11·2%).

By-product (*m. p.* 211—212°).—A 4-hour fusion similar to the above with (I) (14 g., 0·05 mol.) and ammonium benzenesulphonate (44 g., 0·15 mol.) at 255—260° gave, apart from the hydrochloride (m. p. 275—277°) described above, a *by-product* (0·3 g.), m. p. 205—210°, insoluble in methanol, water, hydrochloric acid, or aqueous sodium hydroxide. Crystallisation from alcohol afforded white plates, m. p. 211—212° (Found: C, 83·75, 83·7; H, 6·7, 6·9; N, 8·6, 8·75, 8·75; *N*-Me, 18·75. $C_{22}H_{22}N_2$ requires C, 84·1; H, 7·0; N, 8·9; *N*-Me, 18·5%). Light absorption: Maximum at 2700—2720 Å, $E^{1\%}_{1\,cm.} = 215$; minimum at 2400 Å, $E^{1\%}_{1\,cm.} = 115$; intense end-absorption below 2400 Å.

The authors are indebted to Dr. W. Wilson for information regarding his experimental results and for carrying out the mixed m. p. determinations, and to Mrs. E. Bielski and Drs. Weiler and Strauss for microanalyses. Thanks are also due to Dr. C. H. Kellaway for gifts of chemicals and for kindly affording facilities for *N*-methyl group determinations.

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676. *Colour and Constitution. Part II.* Aromatic Hydrocarbons.*

By M. J. S. Dewar.

An extension of the treatment, applied in Part I * to basic dyes, is described by which the first absorption maxima of aromatic hydrocarbons can be predicted with very little labour. The absorption spectra of such compounds are discussed, and reasons given for identifying the first transition with the first absorption maximum with log ε not appreciably less than 4. The agreement between the predicted and observed wave-lengths of such bands is remarkably good, much better than the agreement with the values predicted by LCAO MO theory (to which the present treatment is a first approximation). A possible explanation of this apparent anomaly is given. Agreement is bad for the peropyrenes; reasons are given for ascribing this failure to an unusually large "fixation" of certain double bonds in them. Agreement also appears to be bad for the compound to which Clar ascribed the structure (I); it is suggested that it may in fact have been the isomer (III), in the event that it proves not to have a band in the infra-red as predicted for (I).

In Part I * a set of rules was derived theoretically for the relation between colour and constitution in odd alternant † ions such as the ions of basic dyes. These rules were obtained by a modification ‡ of the usual LCAO MO method in which perturbation theory was used to estimate approximately the effects of structural changes on the light absorption of such compounds. Such a treatment cannot be applied directly to even alternant systems, like those present in aromatic hydrocarbons and polyenes; but a variation of it will now be described whereby the frequency of the first absorption band (FFAB) of an even alternant hydrocarbon can be calculated with a minimum of labour and with surprising accuracy.

In the PMO (perturbation molecular orbital) method the energy levels of a conjugated molecule RS are calculated from those of R and of S by regarding their combination to RS as a perturbation and applying the familiar methods of perturbation theory. This technique has been used to develop a general semiquantitative theory of chemical reactivity, full details of which are in course of publication (*J. Amer. Chem. Soc.*); here the same procedure will be used to investigate the light absorption of even alternant hydrocarbons.

Method.—In general, the energy difference between RS and (R + S) is a second- and higher-order perturbation energy, the first-order perturbation vanishing. An exception arises in the case where R and S are both odd alternant hydrocarbons; *e.g.*, when R = S = benzyl, RS = stilbene. An odd alternant hydrocarbon has a non-bonding § MO (NBMO) of zero energy in LCAO MO approximation, *i.e.*, an MO of energy identical with that of a carbon 2*p* AO. The degeneracy of the two NBMO's in (R + S) leads to a first-order perturbational splitting of the level in forming RS [if RS is to be a normal even alternant hydrocarbon, the two NBMO's in (R + S) must have contained just two electrons between them; in RS these can be accommodated in the lower of the two MO's corresponding to the original zero-energy NBMO's, and consequently there is a first-order perturbation energy difference between (R + S) and RS].

Suppose the linkages in RS are between atom number *m* in R and atom number *m* in S,

* Part I, *J.*, 1950, 2329.

† In an alternant compound the conjugated atoms can be divided into two sets, "starred" and "unstarred," such that no two atoms of the same set are directly linked. Compounds are excluded from this category only if they contain odd-numbered mesomeric rings (*e.g.*, azulene, fulvene). The special properties of alternant hydrocarbons were first indicated by Coulson and Rushbrooke (*Proc. Camb. Phil. Soc.*, 1940, **36**, 193).

‡ Similar methods have been used by Matsen (*J. Amer. Chem. Soc.*, 1950, **72**, 5243) in a study of the light absorption of benzene derivatives.

§ The term "non-bonding MO" in this connection is due to Longuet-Higgins (*J. Chem. Phys.*, 1950, **18**, 265), who has discussed the properties of such orbitals in detail. See also Coulson and Rushbrooke, *loc. cit.*

atom n in R and atom n in S, etc.; then it can be shown * that, to the approximation of first-order perturbation theory, the NBMO's (of zero energy) of R, S, are replaced in RS by two MO's of energy $\pm E$ with

$$E = \beta(a_m b_m + a_n b_n + \ldots.) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where a_m is the coefficient of the AO of atom m in the NBMO of R, and b_n the corresponding coefficient in the NBMO of S, and β is the C–C resonance integral.† It follows that the difference in total π-electron energy between RS and (R + S) is given to this approximation by $2E$, since the two odd electrons in the NBMO's of (R + S) can both occupy the corresponding bonding perturbed MO in RS of energy $-E$.

Now as a general rule ‡ the union of R and S to form RS alters the energies of the MO's but does not alter their order; so that the highest occupied and lowest unoccupied MO's of RS correspond to the highest occupied and lowest unoccupied MO's in (R + S). In the case we are considering these are the NBMO's of R and of S; hence, to the approximation of first-order perturbation theory, the highest occupied and lowest unoccupied MO's of RS have energies $\pm E$, with E given by equation (1). The FFAB ν_0 of RS should then be given by

$$h\nu_0 = 2E = 2\beta\Sigma_m a_m b_m \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

or equivalently, the wave-length λ_0 of the first absorption bond by

$$\lambda_0 = \frac{c}{\nu_0} = \frac{hc}{2\beta}\left(\Sigma_m a_m b_m\right)^{-1}$$
$$= C\left(\Sigma_m a_m b_m\right)^{-1} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

where C is an empirical constant, since in the simple LCAO method the resonance integral β is determined empirically. (In this argument it is implicitly assumed that the FFAB corresponds to a transition between two π-orbitals, *i.e.*, a π–π transition; this point will be discussed later.)

An ambiguity arises in applying equation (3), since the energy difference E depends on the mode of partition of the even hydrocarbon RS into two odd radicals. That this should be so can be seen clearly from the fact that the difference in π-electron energy between RS and (R + S) will be less, the more stable the radicals R and S, and this energy difference is also given in the present approximation by $2E$.

This ambiguity can be resolved by the following argument. It can be shown that the effect of the second-order perturbations is to reduce the splitting of the two levels in question. If then, as seems reasonable, higher perturbations can be neglected, the value for λ_0 estimated from (3) will necessarily be too small. The best estimate of λ_0 will then be given by that mode of partition of RS which minimises E and so maximises λ_0. A proviso should be added that if any of the R–S bonds in RS link inactive § atoms in R or S, so that the corresponding products $a_m b_m$ vanish, these bonds will not contribute to the first-order perturbation energy E, but they will contribute to the higher-order perturbations which are being neglected. The mode of partition of RS should therefore

* Full details will be found in the forthcoming papers referred to above.

† The usual simplifying assumptions are made that all C–C resonance integrals between adjacent atoms are similar, and that resonance integrals between non-adjacent atoms, and also overlap integrals, can be neglected.

‡ This non-crossing rule holds rigorously if no level of RS is the same as one of R or of S, since it can then be shown (Dewar, *Proc. Camb. Phil. Soc.*, 1949, **45**, 639) that the levels of RS interlace with those of (R + S). The only cases where this condition is not fulfilled are those where a level in R or S is degenerate, or where an MO of R or S has vanishing coefficients at the points of union with S or R respectively in RS. The latter condition seldom arises, and in the cases under consideration here the relevant orbitals of R and of S are non-degenerate.

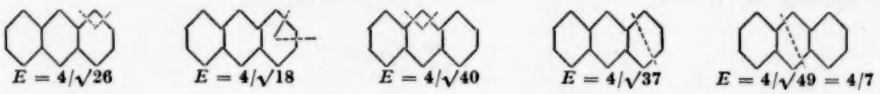
§ If the coefficient of an AO in the NBMO of an odd alternant hydrocarbon vanishes, that atom is called " inactive " (see Longuet-Higgins, *loc. cit.*).

be one in which none of the terms in the summation vanishes, *i.e.*, one in which the uniting bonds are all between pairs of active atoms in R and S.

No general rules can be given for finding this optimum mode of partition; but two guiding principles limit the choice. First, minimising E implies, as we have seen, that the radicals R and S should be the most stable pair into which RS can be dissected; and secondly, the number of terms in the sum, and so the number of bonds broken, should be as small as possible. In all the cases studied, with two exceptions, the optimum partition has involved the breaking of just two bonds.

The NBMO coefficients can be found extremely simply by the method discovered by Longuet-Higgins (*loc. cit.*), and even in the most complex hydrocarbons their calculation can be effected in a few minutes. The labour involved in calculating λ_0 for all the reasonable modes of partition of a given AH (alternant hydrocarbon) is therefore very small.

Example.—The method can be illustrated by an example, *viz.*, anthracene. One would expect the optimum pair of radicals to be one in which two of the three aromatic rings remained intact, other pairs of radicals being less stable; calculation shows in fact that the sum in equations (1)—(3) is appreciably greater for partitions of the latter type. Values of the sum are given below for the remaining five modes; * clearly the optimum mode is that involving partition into two benzyl radicals. Since the corresponding value for benzene is unity, the FFAB's of benzene and anthracene should be in the ratio 7 : 4 (for comparison with observation, see Table 1).



Results.—In this way the FFAB's of the normal fused-ring aromatic hydrocarbons with up to six rings have been calculated together with those of a few hydrocarbons of greater complexity. The corresponding wave-lengths are given (in mμ) in Tables 1 and 2. The constant C in equation (3) was fixed by equating λ_0 for benzene to 208 mμ.† In Table 1 are also given some values for λ_0 found by solving the LCAO MO secular equations, for comparison with the values given by the present approximate treatment and with experiment (these calculations are taken from Pullman and Pullman, "Les Théories Electroniques de la Chimie Organique," Masson, Paris, 1952).

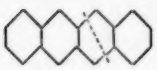
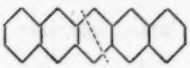
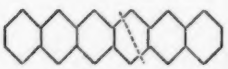
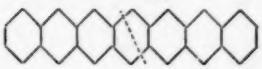
Experimental Values.—The quantities that have been predicted are the wave-lengths of the absorption bands corresponding to the first π–π transitions. As several authors have pointed out (see Pullman and Pullman, *op. cit.*, for references), the simple MO method does not distinguish between singlet and triplet excited states, and consequently the predictions should properly be compared with the means of the transition energies for the first singlet–singlet and singlet–triplet transitions.

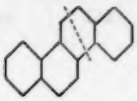
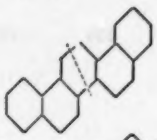
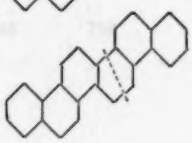
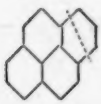
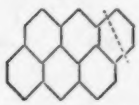
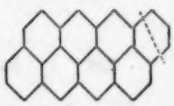
Unfortunately, the singlet–triplet separations are known only in a few cases, and so some method is necessary for deriving such means from the observed singlet–singlet transitions. Some authors (see Pullman and Pullman, *op. cit.*) have assumed that the separations of the first excited singlet and triplet levels are constant, but an alternative assumption would be that the singlet–singlet and singlet–triplet transition energies are proportional to one another. The latter assumption seems to be supported by the values quoted in Table 3 (the singlet–triplet transitions were measured by McClure, *J. Chem. Phys.*, 1951, **19**, 670; the values for the singlet–singlet transitions are discussed below. Note that the singlet–triplet separations are not constant).

* Note that in (*a*)—(*c*) single atoms are detached (formally R or S = methyl). This is legitimate since the 2*p* AO of a methyl radical has the same energy, in this approximation, as a NBMO. The corresponding coefficient in equations (1)—(3) is of course unity.

† In the simple LCAO MO treatment, the first transition in benzene is four-fold degenerate. Inclusion of electron spin removes this degeneracy; so in comparing the calculated and observed values for benzene, the observed value taken should be the mean (208 mμ) of the four corresponding singlet–singlet transitions. This argument is due to Platt (*J. Chem. Phys.*, 1950, **18**, 1168). It so happens that the first intense transition in benzene lies at about the same wave-length.

TABLE 1. *Light absorption of condensed aromatic hydrocarbons.*

Compound [a]	λ_e, calc.: (a) PMO	λ_e, calc.: (b) Secular equation	λ_e, obs.
	(208)	(208)	208
	259	337	275
	364	503	375
	454	618	474
	589	950	581
	714	—	693 [c]
	883	—	—
	328	343	293

Compound [a]	λ_e, calc.: (a) PMO	λ_e, calc.: (b) Secular equation	λ_e, obs.
	308	304	319
	320	439	329
	326	—	340 [b]
	360	467	364
	406	—	433
	588	—	589 [c]

[a] Clar, *Ber.*, 1948, **81**, 63. [b] Private communication from Dr. E. Clar. [c] Clar, *Ber.*, 1943, **76**, 332.
[a] Kekulé double bonds are omitted.

TABLE 2. *Light absorption of condensed aromatic hydrocarbons.*

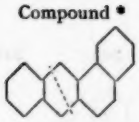
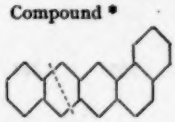
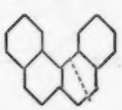
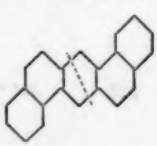
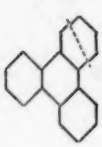
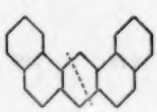
Compound [a]	λ_e, calc. (PMO)	λ_e, obs.	Compound [a]	λ_e, calc. (PMO)	λ_e, obs.
	351	359		482	453
	284	317		346	351
	245	257		319	338

TABLE 2—*continued.*

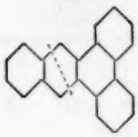
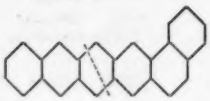
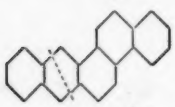
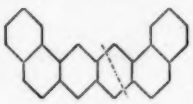
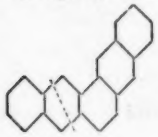
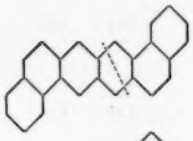
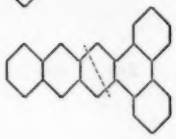
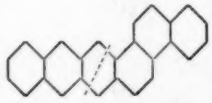
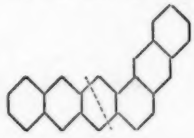
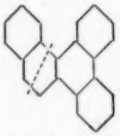
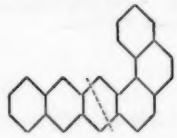
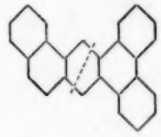
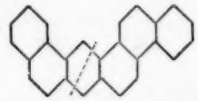
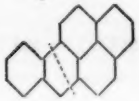
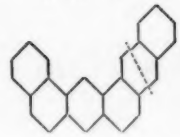
Compound [a]	λ_0, calc. (PMO)	λ_0, obs.	Compound [a]	λ_0, calc. (PMO)	λ_0, obs.
	317	336		546	551 [c]
	368	367		394	438 [d]
	357	348		407	438, 411 [d]
	357	—		378	441, 414 [c]
	302	—		450	—
	296	330 [a]		427	443
	294	—		435	—
	395	434		302	345
	323	331 [b]		332	—
	449	385		355	—

TABLE 2—*continued.*

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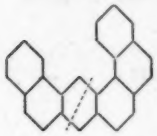
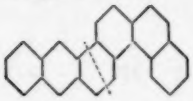
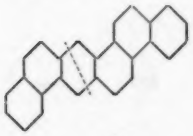
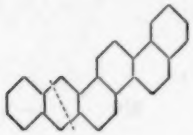
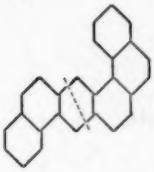
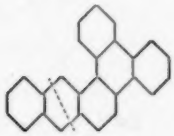
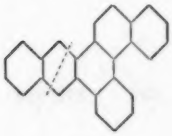
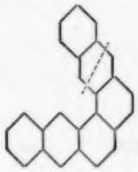
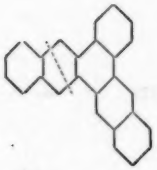
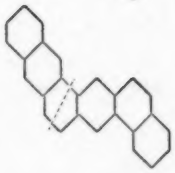
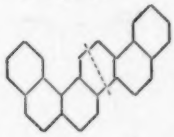
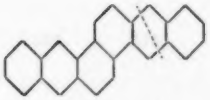
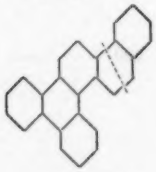
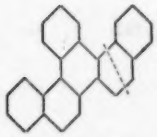
	342	—		340	—
	360	371 [d]		366	—
	350	—		369	—
	330	—		367	—
	317	—		359	—
	354	368		317	—
	380	420		305	—
	344	—		296	—
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TABLE 2—*continued.*

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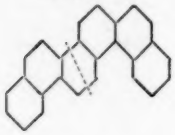
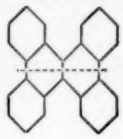
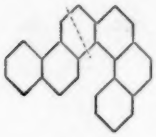
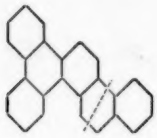
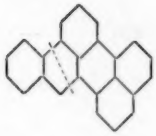
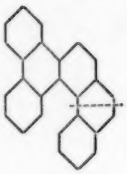
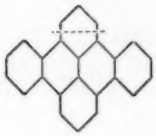
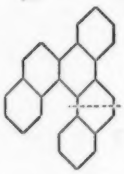
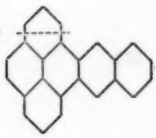
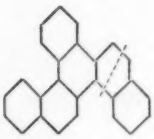
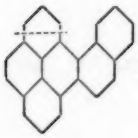
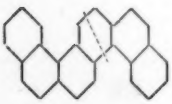
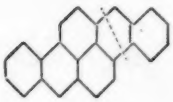
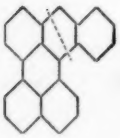
	317	—		347	—
	310	—		305	—
	296	—		444	—
	296	—		299	377, 329[a]
	312	—		321	—
	300	—		349	—
	292	—		512	451
	554	—		416	402[a]

TABLE 2—*continued.*

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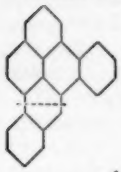
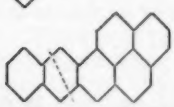
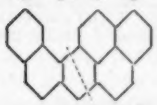
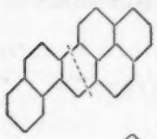
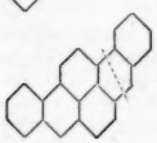
	392	378 [c]
	456	458
	420	—
	456	—
	474	433
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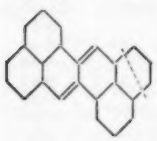
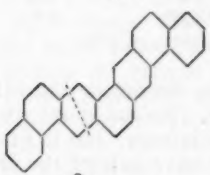
	660 (527)	—
	355	368
	439	433

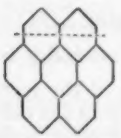
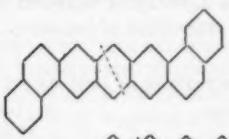
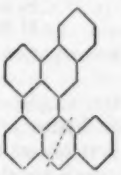
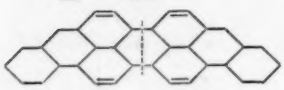
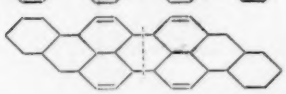
Compound [a]	λ_e, calc. (PMO)	λ_e, obs.
	843	643 (?) [f]
	641	643 (?) [f]
	293	341
	505	516 [g]
	509	529 [h]
	680	582 [i]
	549	503 [j]
	402	402 [j]

TABLE 2—*continued.*

Compound [a]	λ_0, calc. (PMO)	λ_0, obs.	Compound [a]	λ_0, calc. (PMO)	λ_0, obs. [k]
	624 (457)	458 [k]		506	445 [k]
	740 (479)	498 [k]			
	759 (493)	523 [k]			

[a] Bergmann and Szmuszkovicz, *J. Amer. Chem. Soc.*, 1951, **73**, 5150. [b] Clar, *Ber.*, 1943, **76**, 609. *Idem, Ber.*, 1948, **81**, 63. [d] *Idem, Ber.*, 1943, **76**, 151. [e] *Idem, Ber.*, 1948, **81**, 68. [f] Clar and Guzzi, *loc. cit.* [g] Clar and Sandke, *Ber.*, 1949, **82**, 52. [h] Clar, *Ber.*, 1948, **81**, 261. [i] *Idem, J.*, 1949, 2013. [j] *Idem, Ber.*, 1949, **82**, 46. [k] *Idem, Ber.*, 1943, **76**, 458.

If this is true in general, then the first singlet–singlet (E_{11}) and singlet–triplet (E_{13}) transition energies will be related by :

$$E_{13} = kE_{11} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

where k is a constant. The mean, $\overline{E}$, of the two transition energies is then given by

$$E = \tfrac{1}{2}(E_{11} + E_{13}) = \tfrac{1}{2}(1 + k)E_{11} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

The predicted value for E is of the form $x\beta$ [cf. equation (2)] where β is the empirical resonance integral; it follows that the calculated values can be referred directly to singlet–singlet transitions by using a different value β' for the resonance integral with

$$\beta' = 2\beta(1 + k)^{-1} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

This has been done implicitly in Tables 1 and 2, the adjustable parameter in equation (3) being chosen to give agreement between the calculated and observed values of λ_0 for the first singlet–singlet transition of benzene.

TABLE 3. *Comparison of first singlet–singlet and singlet–triplet transition energies.*

Compound.	E_{11} (cm.$^{-1}$)	E_{13} (cm.$^{-1}$)	$(E_{11} - E_{13})$ (cm.$^{-1}$)	E_{13}/E_{11}
Benzene	51,900	29,400 [a]	22,500	0·61
Naphthalene	36,400	21,300	15,100	0·59
Anthracene	26,700	14,700	12,000	0·55
Phenanthrene	34,100	21,600	12,500	0·63
1 : 2-Benzanthracene	32,200	16,500	15,700	0·59
Chrysene	31,400	19,800	11,600	0·63
Triphenylene	38,900	23,800	15,100	0·61
1 : 2-5 : 6-Dibenzanthracene	31,500	18,300	13,200	0·64

[a] Values for E_{13} are those reported by McClure, *J. Chem. Phys.*, 1951, **19**, 670.

The identification of the first singlet–singlet transition presents difficulties, since the study of the spectra of aromatic hydrocarbons is still in its infancy. No ambiguity arises in the polyacenes, where the first absorption bands are invariably intense; but in other cases there are often several weak bands (log $\varepsilon < 3$) to the long-wave side of the first intense band (log $\varepsilon \sim 4$). It is necessary to decide which of these regions of absorption corresponds to the first π–π singlet–singlet transition.

It seems natural on general grounds to identify this with the first intense maximum, since the MO method predicts a large transition moment for the first π–π band (except in the rare cases where the transition is forbidden through symmetry). This assumption is also supported by analogy from a consideration of the vibrational fine structure of the bands. In the polyacenes the first transitions show a regular vibrational structure, apparently corresponding to the fundamental and overtones of a single vibration in each

case, and the spacing is invariably in the range 1100—1500 cm.$^{-1}$. The first intense absorption bands of other aromatic hydrocarbons have a similar fine structure in all cases where it is resolved. The weaker bands at lower frequencies usually show a more complex structure with other vibrations appearing. Since bands of the former type almost certainly correspond to the first normal π–π transitions in the case of polyacenes, where there is no ambiguity, it seems natural to identify the analogous bands of other hydrocarbons with similar transitions.

The origin of the weaker bands would then remain to be elucidated. Possibly an explanation may be found in terms of σ–π interactions of the kind considered by Altmann (*Proc. Roy. Soc.*, 1951, *A*, **210**, 343) and shown by him to provide a possible explanation of the analogous weak band in ethylene near 200 mμ.

There is no reason why in a vibrational band system the zero–zero transition should be the most intense. It is so in the polyacenes, but in 1 : 2-benzanthracene, for instance, the first excited vibrational peak is the highest. The transition energies calculated by MO theory are electronic transition energies, and they should therefore be compared with those observed for zero–zero transitions. This implies, for example, that the "observed" first absorption band of 1 : 2-benzanthracene must be taken to be the first peak at 359 mμ, not the more intense vibrational level at 341 mμ. Since, however, the absorption maxima quoted in the literature commonly correspond to the maxima of the first band systems and not of the first peaks in them, it is important to have the actual absorption spectrum for reference to avoid this ambiguity. The experimental results given in Tables 1 and 2 correspond to the first peak in the first absorption band with log ε not appreciably less than 4; and they are given only for compounds whose absorption spectra have been published. In one or two cases, where there is still ambiguity, values for both peaks are given.

One further complication is the fact that the absorption maxima of hydrocarbons show appreciable solvent effects. Ideally, absorption spectra of the vapours should be used for comparison, but since these are seldom available the data in Tables 1 and 2 refer to solutions (usually in alcohol). The variations due to solvent effects are unlikely to exceed 10 mμ, or at most 20 mμ, and errors of this magnitude are negligible in the present connexion.

Except where explicitly stated the data are taken from Clar ("Aromatische Kohlenwasserstoffe," Berlin, 1941).

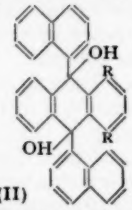
Discussion.—The general agreement between theory and experiment shown in Tables 1 and 2 is astonishingly close, considering the crudity and simplicity of the theoretical methods used. In one respect the agreement is almost embarrassing since the LCAO MO method, to which the present treatment is a first approximation, is unsatisfactory (cf. Table 1). A possible explanation for this curious situation may be suggested. It is known that the failure of the LCAO MO method (in its simple form) is due mainly to its neglect of electron spin and to the resulting lack of antisymmetry in the corresponding molecular wave-functions, and possibly also to its neglect of configurational interaction. Now, it seems likely that in the most complete MO treatment of an odd alternant hydrocarbon radical, when all these factors have been taken into account, it will still appear that the odd unpaired electron occupies something analogous to the NBMO of the simple theory. If then the present perturbation treatment were applied to the formation of RS from (R + S), but with use of the best possible anti-symmetrised MO wave-functions for R and S, instead of simple product wave-functions, the results might not differ significantly from those given by the present simple treatment. In other words, the effects of electron spin, etc., on RS and (R + S) may well be similar so that in the present treatment their effects cancel, and the results obtained are in effect first approximations, not to the simplified MO treatment, but to the antisymmetrised molecular orbital method with configurational interaction.

The general success of the present treatment focuses attention on the few cases where it fails badly. The most interesting of these is the compound formulated by Clar and Guzzi (*Ber.*, 1932, **65**, 1521) as (I). This was obtained by treating (II; R = H) with aluminium chloride, and as the authors themselves pointed out, the chemical evidence that the resulting compound was (I), although suggestive, by no means excluded the isomeric

structure (III).* The predicted first absorption for (III) (641 mμ) agrees almost exactly with that observed (643 mμ) by Clar and Guzzi for their product. On the other hand, they did not study the absorption spectrum beyond 700 mμ, at which point the extinction coefficient was still very high (log $\varepsilon = 3$); and it is possible that there may be an additional band, as predicted for (I), at about 840 mμ. Evidently, the structure and absorption spectrum of Clar's hydrocarbon should be reinvestigated.

Large discrepancies are also observed in the peropyrene series—both in peropyrene itself (IV) and in the two dibenzo-derivatives (V) and (VI). Reasonable agreement is

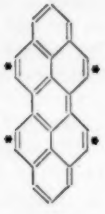
(I)



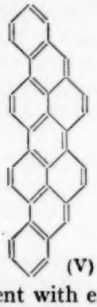
(II)

(III)

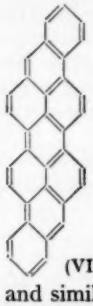
found, however, for the third dibenzo-derivative (VII). Now, the bond orders in (IV) should alternate more than the bond orders in most aromatic hydrocarbons, since each of the lateral bonds [asterisked in (IV)] is double, and each adjacent bond single, in all but one principal resonance form.† The corresponding variations in bond length will alter the C–C resonance integrals. Numerous authors have, of course, considered this effect and devised methods to allow for it (see, *e.g.*, Lennard-Jones, *Proc. Roy. Soc.*, **1937**, *A*, **158**, 280). No attempt will be made to apply any such refined treatment here; but it may be noted that if allowance is made in a crude manner by ascribing values ‡ of 1·09β and 0·91β, respectively, to the " strong " and " weak " bonds in (IV), the calculated value for λ_0 falls



(IV)



(V)



(VI)

(VII)

to 457 mμ in exact agreement with experiment, and similar calculations for (V) and (VI) give values for λ_0 of 479 and 493 mμ, respectively, which are also close to those actually observed. This variation in the C–C resonance integral seems of a very reasonable order of magnitude in view of the magnitude of the alternation in bond order that would be expected in these compounds [the bond orders in (IV) are being calculated by standard methods to test this prediction]. It seems very likely, therefore, that the bond-order effect is real, the more so since a similar explanation will be shown in the following paper to account satisfactorily for the light absorption of the polyenes where the effect becomes very large.

Hence, it might appear that the present method could be improved by calculating (by

* The only evidence adduced was that the 1 : 4-dimethyl derivative (R = Me) of (II), which cannot cyclise to a compound analogous to (I), gave no similar product; and that the hydrocarbon gave an adduct reversibly with maleic anhydride. Both (I) and (III) could add maleic anhydride across the *meso*-positions without stereochemical difficulties arising, and both should react with comparable ease; while the failure of the reaction of (II; R = Me) with aluminium chloride is scarcely significant since (II; R = H) itself reacted to give (I) [or (III)] only under carefully controlled conditions.

† This use of resonance theory can be justified by an argument based on the PMO treatment (Dewar and Longuet-Higgins, *Proc. Roy. Soc.*, in the press), but the same conclusion could in any case be reached by calculating approximately the relevant bond orders, making use of the PMO techniques to which reference was made above.

‡ The values ascribed were actually $\beta \cdot 2^{\frac{1}{2}}$ and $\beta \cdot 2^{-\frac{1}{2}}$ respectively, being chosen by analogy with the values found appropriate for polyenes (see following paper).

the PMO method) approximate bond orders in each hydrocarbon, assuming constancy of the C–C resonance integrals, and then allowing for the changes in those resonance integrals due to the variations in the orders, and so the lengths, of the various bonds in calculating the FFAB by the method indicated here. In view of the crudity of the whole treatment, and of the fact that in the majority of aromatic hydrocarbons the bond orders vary little, such a refinement would be somewhat gratuitous.* It is interesting that even in the case of (V) and (VI), the simple treatment does correctly predict the relative values of the FFAB's and could have been used to distinguish between the isomers if their identities were not already known. Such calculations may therefore be useful in establishing the structures of isomers obtained by ambiguous methods of synthesis [cf. (I) and (III) above].

Appendix

Validity of the Present Use of Perturbation Theory.—This paper forms one of a series in which perturbation methods are being used to build up a general theory of organic chemistry. The mathematical validity of this procedure is not immediately apparent, since it amounts to an expansion of certain energy quantities in powers of resonance integrals which are not small, and there is no guarantee that the leading terms will be dominant. Although the use of perturbation theory in much less satisfactory connections is commonplace (cf. radiation theory, where the higher perturbations are actually known to diverge !), the following partial justification of the present treatment seems of interest since it reduces the empirical element in it.

Consider first the calculation of excitation energies developed in this paper. By using the notation of Part I (*loc. cit.*), and including the second-order perturbation, the excitation energy $2E$ of RS becomes

$$2E = 2a_{or}b_{os}\beta + \sum_{n\neq 0}\frac{a_{or}^2 b_{ns}^2\beta^2}{a_{or}b_{os}\beta - F_n} + \sum_{m\neq 0}\frac{a_{mr}^2 b_{os}^2\beta^2}{a_{or}b_{os}\beta - F_n}$$

$$= 2a_{or}b_{os}\beta\left\{1 - \sum_{n\neq 0}^{\text{occ}}\frac{a_{or}^2 b_{ns}\beta^2}{a_{or}^2 b_{os}^2\beta^2 - F_n^2} - \sum_{m\neq 0}^{\text{occ}}\frac{a_{mr}^2 b_{os}^2\beta^2}{a_{or}^2 b_{os}^2\beta^2 - E_m^2}\right\} \quad . \quad . \quad (7)$$

(The second line follows from the first when use is made of the fact that R and S are both AH's; cf. Part I). Now the mean values of a_{mr}^2 and b_{ns}^2 are approximately $1/n_R$ and $1/n_S$, respectively, where n_R and n_S are the numbers of conjugated atoms in R and S, respectively. The numbers of terms in the sums in (7) are $\frac{1}{2}n_R$ and $\frac{1}{2}n_S$, respectively. As a first approximation, replace the denominators of the terms in (7) by their mean values; then

$$2E \simeq 2a_{or}b_{os}\beta\left\{1 - \frac{a_{or}^2\beta^2}{2(a_{or}^2 b_{os}^2\beta^2 - \bar{F}_n^2)} - \frac{b_{os}^2\beta^2}{2(a_{or}^2 b_{os}^2\beta^2 - \bar{E}_m^2)}\right\} \quad . \quad . \quad (8)$$

where $\bar{E}_m$ and $\bar{F}_n$ are the mean values of E_m and F_n, respectively. Now a_{or}^2 and b_{os}^2 are of the order of $2/n_R$ and $2/n_S$, respectively, while the mean values of E_m^2 and F_n^2 are necessarily $>\beta^2$, and in practice are invariably close to $2\beta^2$. Hence, the ratio of the first- to second-order perturbations is approximately $2n_Rn_S/(n_R + n_S)$, which is always much greater than unity, thus justifying neglect of the latter as a first approximation. Also, the ratio of the first- to second-order perturbations should be greatest, and the first-order perturbation consequently the most accurate, when $(a_{or}^2 + b_{os}^2)$ is a minimum; minimising this expression will normally be equivalent to minimising the first-order perturbation $2a_{or}b_{os}\beta$ as was done in the main body of the paper.

The argument can be extended to cover the use of similar perturbation methods for calculating differences in total π-electron energy. The difference R_{RS} in π-electron energy between RS and (R + S), R and S being even AH's, is given by second-order perturbation theory (Dewar, *loc. cit.*) as

$$R_{RS} = 4\sum_{m}^{\text{unocc}}\sum_{n}^{\text{occ}}\frac{a_{mr}^2 b_{ns}^2\beta^2}{E_m - F_n} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

where $\sum^{\text{occ}}$ and $\sum^{\text{unocc}}$ imply summation over MO's double occupied, or unoccupied, respectively,

* Except in the rare cases where bond fixation is abnormally large; some examples are indicated in Table 2, the wave-lengths calculated with allowance for bond fixation (by the crude method indicated above) being given in parentheses.

in R or S. Now, the mean values of E_m for unoccupied MO's, and of F_n for occupied MO's, are given by

$$\overline{E}_m \text{ (unocc)} = \beta + R_R/n_R \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$
$$F_n \text{ (occ)} = -\beta - R_S/n_S$$

where R_R and R_S are the resonance energies of R and S, respectively, relative to classical structures. The second terms in (10) are the less important, so the mean value of the denominators in (9) is greater than, but not much greater than, 2β. On substitution of mean values for a_{mr}^2 and b_{ns}^2 as before, (9) becomes

$$R_{RS} \simeq \tfrac{1}{2}\beta \ (<\tfrac{1}{2}\beta) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

In practice the resonance energies of even AH's RS relative to pairs of even parts R and S (*e.g.*, of diphenyl relative to benzene + benzene) are closely similar, and somewhat less than $\frac{1}{2}\beta$, in cases where, as assumed in the above analysis, R is singly linked to S in RS (the analysis can be shown to apply also to cases of multiple attachment provided that no additional aromatic rings are formed in the process). The constancy of these energy differences has been noted by Coulson and Longuet-Higgins (*Proc. Roy. Soc.*, 1949, *A*, **195**, 188), who correlate it with the small range of self-polarisibility in even AH's. Note that, owing to the form of the expression in (9), none of the denominators is small, and the total variation in the denominators is never likely to be large; it is therefore not surprising that the denominators can be replaced by mean values without serious error.

If R and S are both odd AH's, there is now a first-order energy difference between RS and (R + S). It can be shown that the total second-order perturbation energy should again be approximately constant, this time slightly less than in the previous case since one relatively important term in the sum necessarily vanishes. Since the first-order perturbations are usually considerably greater than $\frac{1}{2}\beta$, this suggests that the higher perturbations converge and can in any case be replaced, like the second-order perturbations, by mean values. If so, then

$$R_{RS} \simeq C + 2a_{or}b_{os}\beta \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (12)$$

This relation holds quite accurately for a number of cases that have been studied, with $C = 0{\cdot}3\beta$ (Dewar, *J. Amer. Chem. Soc.*, 1952, **74**, 3349).

QUEEN MARY COLLEGE, MILE END ROAD, LONDON, E.1. [*Received, March 29th*, 1952.]

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677. *Colour and Constitution. Part III.* Polyphenyls, Polyenes, and Phenylpolyenes; and the Significance of Cross-conjugation.*

By M. J. S. DEWAR.

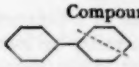
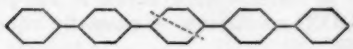
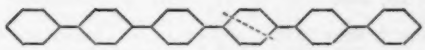
The methods of Part II * are extended to a study of light absorption in polyphenyls, polyenes, and phenylpolyenes. It is found, as suggested in Part II, that allowance must be made for changes in C–C resonance integrals with bond length in hydrocarbons where the bond orders vary greatly. When such allowance is made in a very simple manner, the observed and calculated wave-lengths (λ_0) of the first absorption bands agree remarkably well. An expression is derived for λ_0 in polyenes in terms of the number (N) of conjugated double bonds which agrees much better with experiment than does the currently accepted square-root relationship. The significance of cross-conjugation is analysed, and the currently accepted rule for the light absorption of cross-conjugated alternant hydrocarbons is thereby derived.

A METHOD was described in Part II* whereby the frequency of the first absorption band (FFAB) of an even alternant hydrocarbon (even AH) could be calculated in a simple manner; and the predictions so made for a wide range of condensed aromatic hydrocarbons were shown to agree well with experiment. Here the method is extended to the polyphenyls, polyenes, and phenylpolyenes.

* Part II, preceding paper.

(a) p-*Polyphenyls.*—The method of Part II can be applied directly to the *p*-polyphenyls, and in Table 1 values for λ_0 (the wave-lengths of the first absorption band, in mμ) so calculated [col. (*a*)] are compared with experiment. The constant *C* of equation (3) in Part II was assumed to have the value found appropriate for condensed aromatic hydrocarbons. The optimum modes of bisection of the *p*-polyphenyls are also indicated.

TABLE 1.

Compound * and mode of bisection	λ_0, calc.: (*a*)	(*b*)	λ_0, obs.†
	244	257	252
	286	296	280
	296	302	300
	306	310	310
	308	311	318

* Kekulé double bonds are omitted.
† Experimental data from Braude, *Ann. Reports*, 1945, **42**, 111.

The agreement with experiment is remarkably good. At the same time the use of a single value for β (the C–C resonance integral) is suspect, since the bonds between the phenyl groups must be longer than the intra-annular bonds. However, if allowance is made for this effect [see Section (b)], and the constant *C* adjusted slightly, the values of col. (*b*) in Table 1 are obtained; these are still in excellent agreement with experiment.

(b) *Unbranched Polyenes.*—The same method can be applied very simply to a linear polyene with $2N$ conjugated carbon atoms (*i.e.*, N double bonds in the classical formulation). Suppose the dissection be into odd AH radicals with $(2m - 1)$ and $(2n - 1)$ conjugated atoms, so that

$$m + n = N + 1 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

It is easily shown that the terminal NBMO coefficients in the radicals are $m^{-\frac{1}{2}}$ and $n^{-\frac{1}{2}}$, respectively; hence from equation (3) of Part II,

$$\lambda_0 = C(mn)^{\frac{1}{2}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

when m and n have been chosen to maximize $(mn)^{\frac{1}{2}}$. The maximum value is given when m and n are equal (N odd), or $m - n = \pm 1$ (N even). With N odd, we then have

$$\lambda_0 = \tfrac{1}{2}C(N + 1) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

and the same expression holds to a good approximation with N even. Thus λ_0 should vary linearly as N. A similar linear dependence has been deduced by an alternative approximate MO treatment by Herzfeld and Sklar (*Rev. Mod. Phys.*, 1942, **14**, 294), and it also follows from Kuhn's simple uniform potential model (cf. *J. Chem. Phys.*, 1949, **17**, 1198); but in actual fact λ_0 varies much less rapidly with N.

Kuhn (*loc. cit.*) has ascribed this discrepancy to the large alternation in bond order of alternate bonds in a polyene, the corresponding variation in length being much greater than for bonds in typical aromatic hydrocarbons or in the odd alternant systems of typical basic dyes. By segregating the "single" and "double" bonds and allowing for the differences between them, he has been able to derive the square-root relationship (4) from the uniform potential model:

$$\lambda_0 = kN^{\frac{1}{2}} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

The same expression has been deduced by Lewis and Calvin (*Chem. Reviews*, 1939, **25**, 237) by a classical argument of little theoretical significance. Equation (4) holds accurately for the lower polyenes, but it fails progressively with increasing chain length.

In view of the close connexion between the uniform potential model and the LCAO MO method (Simpson, *J. Chem. Phys.*, 1948, **16**, 1124), it seems natural to ascribe the derivation of the incorrect relation (3) to the over-simplified assumption that all C–C resonance integrals in a polyene are similar; the more so since it was found in Part II that a similar discrepancy arose in the case of certain aromatic hydrocarbons (peropyrene and its derivatives), where the bond orders were predicted to show unusually large variations, and where by ascribing slightly modified resonance integrals to the "fixed" single and double bonds, agreement between observation and theory could be restored.

Assume, then, as a first approximation that all the "double" bonds in a polyene are equivalent, and also all the "single" bonds; but that different values must be ascribed to the resonance integrals of bonds of the two dissimilar types.* Let these values be $a\beta$ and $a^{-1}\beta$, respectively, with $a > 1$. Here a is to be regarded as an additional parameter to be determined empirically. Consider the odd AH with $(2m - 1)$ conjugated atoms obtained by bisection of the $2N$-atom polyene. It is, of course, assumed that the bonds in this radical have the same resonance integrals as corresponding bonds in the parent polyene. The general rule for calculating the NBMO coefficients is given by equation (5) (Longuet-Higgins, *J. Chem. Phys.*, 1950, **18**, 265)

$$a_r\beta_{,r} + a_s\beta_{ps} + a_t\beta_{pt} = 0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

where a_n is the NBMO coefficient of atom n, and β_{pq} the resonance integral of the bond between atoms p and q. On application of (5) to the odd AH with $(2m - 1)$ conjugated atoms, in which alternate bonds have resonance integrals $a\beta$ and $a^{-1}\beta$, the NBMO coefficients are seen to be:

$$\begin{array}{llllll} A & -Aa^2 & Aa^4 & & A(-a^2)^{m-1} & \\ \text{C=C—C=C—C=} & & & & =\text{C—C} & \end{array} \quad . \quad . \quad . \quad . \quad . \quad (6)$$

where the normalizing factor A is given by

$$A = (\sum_{r=0}^{m-1} a^{4r})^{-\frac{1}{2}} = (a^4 - 1)^{\frac{1}{2}}(a^{4m} - 1)^{-\frac{1}{2}} \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

Similar expressions are obtained for the NBMO coefficients of the odd AH with $(2n - 1)$ atoms, n replacing m in (6) and (7). Substitution of the values for the terminal coefficients into equation (3) of Part II gives

$$\lambda_0 = C(a^{4m} - 1)^{\frac{1}{2}}(a^{4n} - 1)^{\frac{1}{2}}(a_4 - 1)^{-1}a^{1-2N} \quad . \quad . \quad . \quad . \quad . \quad (8)$$

The optimum mode of bisection of the polyene is again that which makes $(m - n)$ zero or unity. If N is odd, equation (8) then becomes:

$$\begin{aligned} \lambda_0 &= C(a^{2N+2} - 1)(a^4 - 1)^{-1}a^{1-2N} \\ &= D(1 - a^{-2N-2}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \end{aligned} \quad (9)$$

where the constant D is defined by

$$D = a^3C(a^4 - 1)^{-1} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

If N is even, equation (9) still holds to a good approximation. The parameter a was assumed † to be given by

$$a = 2^{\frac{1}{4}} \simeq 1{\cdot}09 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

* Calculations by the MO method imply that the alternation in bond lengths in a long polyene should decrease rapidly towards the middle of the chain (see Coulson, *Proc. Roy. Soc.*, 1939, *A*, **169**, 413). The quantitative reliability of these calculations is, however, uncertain, since the empirical method used to estimate the variation in the C–C resonance integral with bond length is open to criticism and since no experimental data are available for comparison with theory except for short polyenes where the alternations in bond length are in any case large. The success of the MO method in the case of polycyclic aromatic hydrocarbons is irrelevant in the present connection in view of the dissimilarity of such compounds to polyenes and the small alternations in the lengths of bonds in them. The available chemical and physical evidence seems to suggest that the alternation in bond length in polyenes will prove greater than that predicted by the MO method in the investigation referred to above. The present treatment implies that the mean difference in length between "double" and "single" bonds should be about 0·05 Å, if reliance can be placed in the empirical method for estimating the variation in β with bond length (see Mulliken, Rieke, and Brown, *J. Amer. Chem. Soc.*, 1941, **63**, 48).

† The parameters a and D are of course to be determined empirically, as is β in the usual LCAO treatment.

and the parameter D of equation (9) was chosen to give agreement between theory and experiment for butadiene. The values so calculated are given in col. 3 of Table 2. Experimental values for λ_0 are given in the col. 4. These require some comment since the values are maxima of the first strong system of bands, no account being taken of fine structure (cf. Part II). In the lower members of the series the fine structure is not resolved, and in any case its origin is by no means certain; so this procedure seems the best available. The values for λ_0 refer to solutions in alcohol or paraffin hydrocarbons, the absorption maxima of polyenes being similar in these solvents, and are taken from Karrer and Eugster (*Helv. Chim. Acta*, 1951, **34**, 1805) and Braude (*loc. cit.*). In the last column of Table 2 are given values of λ_0 calculated from the square-root relationship (4) the constant being also adjusted to give agreement for butadiene.

TABLE 2.

		λ					λ		
		From		From			From		From
N	Polyene	(9)	Obs.	(4)	*N*	Polyene	(9)	Obs.	(4)
1	Ethylene	157	163	154	12	Dehydro-β-carotene	480	475	532
2	Butadiene	(217)	217	(217)	13	Decapreno-ε_1-carotene ...	489	495	553
3	Octatrienol	268	265	266	14	Anhydroeschscholtz-xanthin	497	500	574
4	*iso*Axerophthene	310	308	307					
5	Axerophthene	345	346	343	15	Dehydro-β-lycopene	503	504	594
6	Anhydro-vitamin A ...	376	371	376	16	—	508	—	614
7	—	402	—	406	17	—	513	—	632
8	Dihydro-β-carotene ...	422	420	434	18	—	517	—	650
9	ε_1-Carotene	441	439	460	19	Dodecapreno-β-carotene...	520	531	668
10	α-Carotene	456	445	485	20	—	522	—	686
11	γ-Carotene	469	462	509	∞	—	536	—	∞

(c) *Discussion of Sections* (a) *and* (b).—The agreement between the experimental values for λ_0 and those calculated from equation (9) is remarkable; it is well within the limits of variation of λ_0 due to the effects of alkyl substituents or changes in solvent (cf. Part II), neither of which was considered in the calculation. Note once again that the full MO treatment (neglecting electron spin) breaks down completely in the calculation of excitation energies both in the polyphenyls and in the polyenes; a possible explanation of this curious situation was given in Part II. Note also that no satisfactory relation has previously been found between N and λ_0, even empirically.

The values for λ_0 for the lower polyenes calculated from (9) agree very closely with those calculated from the square-root expression (4); but the two expressions diverge progressively when $N > 7$. Equation (9) predicts that λ_0 should tend to a limit as $N \rightarrow \infty$. The experimental evidence evidently favours (9), particularly when it is realized that the only known examples of higher polyenes are those with numerous alkyl substituents, and the bathochromic effect of these has been ignored in comparing observed and predicted values of λ_0.

The empirical value for the ratio of " double " and " single " bond resonance integrals is comparable to that assumed in Part II for peropyrene; this supports the explanation given there for the discrepancy between the observed and predicted FFAB's. The ratio also seems reasonable from theoretical estimates of the variation of β with bond length.

The value assumed for D in equation (9) is nearly 20% less than that calculated from equation (10) by using the value of C found appropriate for aromatic hydrocarbons and *p*-polyphenyls. This discrepancy is disappointing but not surprising; apart from the dissimilarity between aromatic and aliphatic C–C π-bonds, Frank–Condon effects must be much greater in polyenes than in aromatic systems and these should reduce λ_0 and so also D in equation (9). It should be added that agreement between theory and experiment even to within ±20% would have been highly gratifying in view of the much greater discrepancies given by the usual MO method; disappointment arises only because the predictions from equation (9) are so extraordinarily successful when D is suitably chosen.

(d) *Phenyl- and Diphenyl-polyenes.*—The same methods can be used for phenyl- and diphenyl-polyenes, by accepting the values β, $a^{-1}\beta$, and $a\beta$ respectively for resonance

integrals between ring carbons and between " singly " bound and " doubly " bound polyene is by fission of the polyene chain at or near its mid-point (cf. the polyenes), and of the first three phenylpolyenes into (benzyl + methyl), (benzyl + allyl), and (phenylallyl + allyl) respectively. The choice of C in calculating from equation (3) of Part II is ambiguous, since different values have been found appropriate for aromatic compounds on the one hand, and polyenes on the other. Values for λ_0 corresponding to both values of C are compared with experiment in Table 3 (the experimental values are from Braude, *loc. cit.*).

TABLE 3

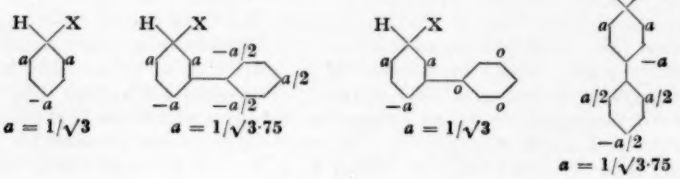
Compound	λ_0, calc. with: aromatic C	polyene C	λ_0, obs.
Styrene	244	201	250
1-Phenylbutadiene	318	261	299
1-Phenylhexatriene	366	301	—
Stilbene	311	256	295
Ph·[CH:CH]$_n$·Ph; $n = 2$	357	294	328
" $n = 3$	412	339	349
" $n = 4$	445	366	375
" $n = 5$	480	395	403
" $n = 6$	505	416	420
" $n = 7$	532	438	435

On intuitive grounds one might have expected the polyene value for C to be appropriate in the limiting case when the polyene chain forms the greater part of the molecule, and intermediate values to hold for the lower polyenes where the molecule is largely aromatic. The results in Table 3 are in good agreement with this idea: the observed values for λ_0 agree closely with those calculated from " polyene C " for the higher diphenylpolyenes, but show a progressive divergence as the polyene chain diminishes in length. carbons, with a given by (11). The optimum mode of dissection of the diphenylpolyenes In styrene and stilbene, the " aromatic C " values for λ_0 agree quite well with experiment, and the agreement is excellent for diphenyl itself (Table 1).

(e) *Cross-conjugation.*—Before discussing the light absorption of hydrocarbons commonly described as cross-conjugated, it is first necessary to examine the definition and significance of cross-conjugation.

Consider, first, the case of an odd AH. It has been shown elsewhere (Dewar, *J. Amer. Chem. Soc.*, 1952, **74**, 3340) that the chemistry of such compounds is dominated by the properties of their NBMO's. Suppose such a compound to be " starred " (Coulson and Rushbrooke, *Proc. Camb. Phil. Soc.*, 1940, **36**, 193) so that the AO's in the NBMO belong to the starred set; and suppose further that not all the starred atoms are active (an active atom being one the coefficient of whose AO in the NBMO differs from zero). Then removal of the inactive segment of the molecule, *i.e.*, the part containing only inactive starred atoms, will not affect the NBMO, and so will not affect the chemical behaviour of the parent odd AH.

Consider, for example, the transition states for substitution in benzene, and in the *o*-, *m*-, and *p*-positions of diphenyl; according to Wheland (*J. Amer. Chem. Soc.*, 1942, **64**, 900) these are odd AH's, and the relative rates of substitution by a given reagent should run parallel to the differences in total π-electron energy between them and the parent hydrocarbons. These energy differences can be related (Dewar, *loc. cit.*) to the coefficients of AO's in their NBMO's, the coefficients being given below:



NBMO Coefficients in transition states for substitution in benzene and diphenyl.

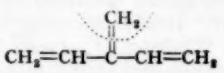
In the transition state for *m*-substitution in diphenyl, the phenyl group is inactive; it should consequently have no effect on the rate of substitution. In the isomeric transition states the phenyl group is active, and can be shown to accelerate the reaction.

This phenomenom, the redundance of part of a mesomeric system, is usually described as cross-conjugation; the present discussion leads to the definition : * *An odd AH is cross-conjugated if not all the starred atoms in it are active.*

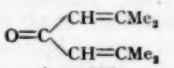
It can be shown that this definition is equivalent in effect to that given by resonance theory, from a correspondence that has been found to exist (Dewar and Longuet-Higgins, *Proc. Roy. Soc.*, in the press) between the resonance theory and the MO method.

In chemical applications, cross-conjugation is important only in odd alternant systems; its apparent influence on the chemistry of even systems is due to the fact that the reactions of such compounds commonly proceed through odd transition states, and in such cases it is the odd transition states that are directly affected (cf. substitution in diphenyl, discussed above). The same is true in the present treatment of the light absorption of even AH's, since it has been related to the properties of pairs of odd AH's into which the even AH's can in principle be divided. It is, however, clear that if an even AH cannot in any way be divided into a pair of non-cross-conjugated odd AH's, then it will be predicted to have the same FFAB as some analogous even AH with fewer conjugated atoms. It is convenient then to define such even AH's as being themselves cross-conjugated : *An even AH is cross-conjugated if it cannot be divided into two non-cross-conjugated odd AH's.*

This definition differs somewhat from those given by current theories; thus the hydrocarbon (III) is not cross-conjugated by the present definition since it can be divided as indicated into two non-cross-conjugated odd AH's. The analogous ketone (IV) does, in fact, absorb at appreciably lower frequencies than its lower analogue (V), implying that (IV) is not cross-conjugated; whereas the light absorption of derivatives of 2 : 3-diphenylbutadiene, which is cross-conjugated by the present definition also, closely resembles that of analogous styrene derivatives (Braude, *J.*, 1949, 1902).

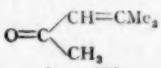


(III)



$\lambda_0 = 259$

(IV)



$\lambda_0 = 230$

(V)

From these arguments a general principle may be derived. Division of a cross-conjugated even AH R gives two odd AH's, one or both of which contain *inactive segments* (i.e., segments containing no active atoms). Removal of these inactive segments would leave two non-cross-conjugated odd AH's which could combine to an even non-cross-conjugated AH R′. It is evident that the values of λ_0 calculated from equation (3) of Part II with this particular mode of bisection of R and R′ will be identical, since the inactive segments in no way affect the NBMO coefficients. The best approximation to the FFAB of R will then be given by the mode of bisection which maximises λ_0 for R′; hence follows the rule : *The FFAB of a cross-conjugated even AH is the same as the least FFAB of any non-cross-conjugated even AH contained in it.*

This rule again corresponds closely to current intuition, except that the definition of cross-conjugation is slightly different.

(f) *Even Cross-conjugated AH's : the* m-*Diphenylyls.*—The *m*-diphenylyls are cross-conjugated according to the present definition, and the largest non-cross-conjugated unit present in them is diphenyl. All should have FFAB's similar to diphenyl itself, and it is well known that they do, up to the highest member of the series yet prepared in which there are no less than 16 benzene rings (Braude, *loc. cit.*).

Conclusions.—These results consolidate the conclusion reached in Part II (*loc. cit.*), *viz.*, that quite satisfactory estimates of FFAB's and AH's can be obtained by the PMO

* A system containing hetero-atoms is cross-conjugated if the equivalent, or isoconjugate, AH is cross-conjugated.

method in spite of its crudity and simplicity. In certain cases such calculations may prove of some practical value since they can be carried out with no effort and in a very short time. The success of the method also raises some interesting theoretical problems, the solution of which may throw a new light on the significance of the molecular orbital approximation.

QUEEN MARY COLLEGE, MILE END ROAD, LONDON, E.1. [*Received, March 29th*, 1952.]

678. *The* S_N *Mechanism in Aromatic Compounds. Part II.**

By JOSEPH MILLER.

A wide range of substituent effects has been surveyed. Substituent rate factors are defined and the results are expressed in terms of these factors.

THE structure of aromatic compounds with the π-electrons distributed in molecular orbitals externally to the ring framework of σ-bonded atoms leads to the commonly observed attack by electrophilic reagents. That suitable substituents or ring hetero-atoms may lead to attack by nucleophilic reagents has been known for many years; *e.g.*, Pisani (*Compt. rend.*, 1854, **39**, 852) recorded the attack by water and ammonia on picryl chloride.

Since the activation consists in denuding a point or points in the ring of the shielding π electrons, activating groups are electron-attracting, particularly those operating by the tautomeric mechanism since then the very important electromeric effects operate, and further such groups stabilise the *cyclo*pentadiene anion type structure of the transition state (see Part I*). The S_N2 mechanism follows from this since the S_N1 heterolysis can only be facilitated by electron-repelling groups and thus a highly electronegative replaced group is required; S_N1 reactions in this field are therefore comparatively rare.

The kinetics of aromatic nucleophilic substitutions have received considerable attention particularly the halogenonitrobenzenes (Holleman *et al.*, *e.g.*, *Rec. Trav. chim.*, 1901, **20**, 292; 1916, **35**, 1; 1928, **47**, 329; 1933, **52**, 428, 901), and there have been many other references covering a wide field (*e.g.*, Singh and Peacock, *J. Phys. Chem.*, 1936, **40**, 669; Bennett and Vernon, *J.*, 1938, 1783; Mangini and Frenguelli, *Gazzetta*, 1939, **69**, 86; Bunnett and Levitt, *J. Amer. Chem. Soc.*, 1948, **70**, 2778; Brady and Cropper, *J.*, 1950, 507; Sugden and Willis, *J.*, 1951, 1380; Spitzer and Wheland, *J. Amer. Chem. Soc.*, 1940, **62**, 2996). Reactions of this type have been reviewed recently by the author (Part I *) and by Bunnett and Zahler (*Chem. Reviews*, 1951, **49**, 273). The latter list an order of substituent groups, and the former, on the basis of the known polar effects of groups (Ingold, *Rec. Trav. chim.*, 1929, **48**, 810), divides substituents into seven main classes. The present paper is a survey of some important substituent groups, ranging from powerful activating to powerful deactivating groups; further parts will deal with individual groups and sub-groups.

In order to gauge uncomplicated substituent effects, *para*-substituents are preferred. However, in order to obtain reasonable rates of attack in the temperature range 0—100°, it is necessary in many cases to have activating groups present. In the work now described, therefore, activating groups (NO_2) have always been present in the *ortho*-position(s), and the *p*-substituents have been varied. Further, the replaced group has always been chloro, the attacking reagent sodium methoxide, and the solvent dry methanol.

The substituent groups investigated have been NO_2, CO_2Me, CO_2^-, CH_3, Cl, NH_2. The compounds studied were (i) *o*-chloronitrobenzene, (ii) *p*-chloronitrobenzene, (iii) 2-chloro-1 : 3-dinitrobenzene, (iv) 1-chloro-2 : 4-dinitrobenzene, (v) methyl 4-chloro-3 : 5-dinitrobenzoate, (vi) 4-chloro-3 : 5-dinitrobenzoic acid, (vii) 4-chloro-3 : 5-dinitrotoluene, (viii) 2 : 5-dichloro-1 : 3-dinitrobenzene, and (ix) 4-chloro-3 : 5-dinitroaniline.

In this preliminary paper only sufficient activation energies are presented to give numerical values of the "substituent rate factor" (S.R.F.), *i.e.*, the ratio of the rates of reaction, Ar'X/ArX, with the same reagent R and at the same temperature, where Ar' differs from Ar only in that a hydrogen atom has been replaced by a substituent group. By definition the S.R.F. of H = 1.

* *Rev. Pure Appl. Chem.*, 1951, **1**, 171, is regarded as Part I.

The values obtained are given in Table 1.

TABLE 1.

$10^5 k_2$, measured or, where shown in parentheses, calc. from Arrhenius parameters

Compound [a]	0·0°	15·0°	25·0°	26·35°	30·2°	35·0°	71·0°	75·3°	81·6°	100·8°
(i)	(0·0$_3$323)	—	—	—	(0·0240)	—	—	3·62	6·82	37·4
(ii)	(0·0$_2$920)	—	—	—	(0·0741)	—	8·42	—	23·5	137·3
(iii)	(3·61)	—	—	90·5	138	226	—	—	(15,700)	—
(iv)	200	1060	2960	—	(4890)	—	—	—	(322,500)	—
(v)	3610	—	—	—	—	—	—	—	—	—
(vi)	57·0	—	—	—	—	—	—	—	—	—
(vii)	—	—	—	—	18·6	—	—	—	—	—
(viii)	51·8	—	—	—	—	—	—	—	—	—
(ix)	—	—	—	—	—	—	—	—	23·0	—

Compound [a]	Substituent	S.R.F. at 0·0°	S.R.F. at 30·2°	S.R.F. at 81·6°	S.R.F. (calc. from results of other workers)
(i)	—	—	—	—	—
(ii)	—	—	—	—	—
(iii)	*o*-NO_2	$1·12 \times 10^4$	$5·75 \times 10^3$	$2·30 \times 10^3$	$1·17 \times 10^3$ at 85° [c]
(iv)	*o*-NO_2	$2·17 \times 10^5$	$6·59 \times 10^4$	$1·37 \times 10^4$	$2·81 \times 10^4$ at 85° [c]
	p-NO_2	$6·19 \times 10^5$	$2·04 \times 10^5$	$4·73 \times 10^4$	$7·55 \times 10^4$
(v)	*p*-CO_2Me	$1·00 \times 10^3$	—	—	—
(vi)	*p*-CO_2^-	$1·58 \times 10^1$	—	—	$1·54 \times 10^1$ at 25° [b]
(vii)	*p*-CH_3	—	$1·35 \times 10^{-1}$	—	$1·76 \times 10^{-1}$ at 50° [c]
(viii)	*p*-Cl	$1·43 \times 10^1$	—	—	8·65 at 0° [c]
(ix)	*p*-NH_2	—	—	$1·46 \times 10^{-3}$	—

[a] Holleman *et al.*, *Rec. Trav. chim.*, 1916, **35**, 1; 1920, **39**, 435. [b] Rouche (*Bull. Acad. Sci. roy. Belg.*, 1921, 534) with a mononitrofluorobenzoic acid. [c] Bevan, Hughes, and Ingold (unpublished; quoted by Bunnett and Zahler, *loc. cit.*), using sodium ethoxide in ethanol.

[a] For numbered compounds, see p. 3550.

Since the rate of attack on the monohalogenobenzenes has not yet been measured in the present work, the values for *o*- and *p*-chloronitrobenzene can give only the ratio *p*-NO_2/*o*-NO_2 in the absence of other substituents. This value varies from 3·45 at 81·6° to 3·67 at 100·8°; it may be compared with the value obtained by Holleman *et al.* (*locc. cit.*), *viz.*, 3·72 at 85°.

The rate constants for *o*- and *p*-chloronitrobenzene and 1-chloro-2 : 4- and 2-chloro-1 : 3-dinitrobenzene give good straight-line plots of $\log_{10} k_2$ against $1/T$. From these are obtained values of activation energies (E) and frequency factors (B) given in Table 2. Holleman's values (*loc. cit.*, 1916) are also shown; the latter are for two temperatures only except for 1-chloro-2 : 4-dinitrobenzene, for which, however, the values do not give a straight line.

TABLE 2.

Compound	E (cal.)	$\log_{10} B$	(Holleman *et al.*) E (cal.)	(Holleman *et al.*) $\log_{10} B$
o-Chloronitrobenzene	23,500	10·30	23,200	12·0
p-Chloronitrobenzene	23,950	11·12	23,000	12·5
2-Chloro-1 : 3-dinitrobenzene	19,770	11·37	17,900	11·8
1-Chloro-2 : 4-dinitrobenzene	17,430	11·26	16,800	12·5

The values in Table 2 are sufficient for calculation of the S.R.F.s of *p*-substituents, and also include values for the *o*-nitro-group. Most compounds were directly compared with 2-chloro-1 : 3-dinitrobenzene and the steric effects are constant. 1-Chloro-2 : 4-dinitrobenzene may be compared with both *o*- and *p*-chloronitrobenzene to give the S.R.F. of both *o*- and *p*-NO_2 groups, and comparison of 2-chloro-1 : 3-dinitrobenzene with *o*-chloronitrobenzene gives the S.R.F. of an *o*-NO_2 group when another such group is already present. The ratio *p*-NO_2/*o*-NO_2 at 81·6° then becomes 20·6. This will be discussed in a later paper.

The S.R.F. values obtained show that substituent effects are very large, and will be sensitive to small variations in group-activating power. Although the groups chosen do not cover the complete range accessible through compounds prepared with reasonable facility, the S.R.F.s already measured cover a range of more than 3×10^7.

The results are in agreement with the activating powers of substituents predicted by the author (Part I, *loc. cit.*).

Experimental

Thermostats were controlled to ±0·02° or better. The methanol used was dried by distilling it once from concentrated sulphuric acid then twice from aluminium amalgam through a column. It was tested for moisture content by Weaver's method (*J. Amer. Chem. Soc.*, 1914, **36**, 2463), and shown to contain not more than 0·001%.

A typical run is for 2-chloro-1 : 3-dinitrobenzene at 26·35°, shown herewith.

Titre (ml.)	$10^5(b-x)$ (moles/l.)	$10^5(a-x)$ (moles/l.)	t (sec.)	10^4k_2	Titre (ml.)	$10^5(b-x)$ (moles/l.)	$10^5(a-x)$ (moles/l.)	t (sec.)	10^4k_2
4·96	7935	4662	0	—	8·58	6106	2833	8,100	8·897
5·24	7795	4527	422	9·168	9·50	5641	2368	11,220	9·154
5·49	7670	4397	832	8·964	10·08	5348	2075	13,860	9·137
5·72	7552	4279	1190	9·282	10·69	5039	1766	17,100	9·231
6·02	7400	4127	1790	8·883	11·15	4808	1535	20,400	9·132
6·34	7238	3965	2400	8·913	11·54	4612	1339	23,700	9·085
6·99	6910	3637	3715	9·094	11·95	4405	1132	28,260	8·941
7·45	6678	3405	4800	9·010	14·19 }	3273	0	—	—
7·90	6451	3178	6005	8·966	14·19 }				

Average value: $k_2 = 9{\cdot}05 \times 10^{-4}$ l. mole^{-1} sec.$^{-1}$.

Preparation of Materials.—*o*- and *p*-Chloronitrobenzene and 1-chloro-2 : 4-dinitrobenzene were commercial products, purified by recrystallisation, and had m. p.s 32·5°, 83°, and 50·5°, respectively. 2-Chloro-1 : 3-dinitrobenzene was made from chlorobenzene in four stages, the first according to Lindemann and Wessel (*Ber.*, 1925, **58**, 1221) and the others according to Welsh (*J. Amer. Chem. Soc.*, 1941, **73**, 3276). The final product had m. p. 87°. 4-Chloro-3 : 5-dinitrobenzoic acid and its methyl ester were prepared from *p*-chlorobenzoic acid by Ullmann and Kuhn's method (*Annalen*, 1909, **366**, 92). The final products had m. p. 160° and 105°, respectively. 4-Chloro-3 : 5-dinitrotoluene was prepared in three stages from aceto-*p*-toluidide; the first two stages were according to Brady, Day, and Rolt (*J.*, 1921, **121**, 521), and the last was a Sandmeyer reaction, nitrosylsulphuric acid being used as diazotising agent. The final product had m. p. 114—115°. 2 : 5-Dichloro-1 : 3-dinitrobenzene was prepared by dinitration of *p*-chlorophenol by concentrated sulphuric and nitric acids, followed by substitution of chloro for hydroxy according to Ullmann and Sane (*Ber.*, 1911, **44**, 3731). The final product had m. p. 105°. 4-Chloro-3 : 5-dinitroaniline was made from the corresponding acid *via* the chloride and azide (Lindemann and Wessel, *loc. cit.*).

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University of Western Australia, Nedlands, W.A. [*Received, April 1st*, 1952.]

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679. *The* S_N *Mechanism in Aromatic Compounds. Part III.**

By Athelstan L. Beckwith, Joseph Miller, and (in part) Gerard D. Leahy.

The reactions of 1-halogeno-2 : 4-dinitrobenzenes with sodium methoxide or sodium *p*-nitrophenoxide in absolute methanol have been examined quantitatively and shown to agree with the predictions made in Part I (Miller, *Rev. Pure Appl. Chem.*, 1951, **1**, 171). The variation of activation energies and frequency factors is discussed.

The variation in the rate of nucleophilic replacement of chlorine, bromine, and iodine has received much study in both the aliphatic and the aromatic series (*e.g.*, Hughes and Ingold, *J.*, 1935, 244, and subsequent papers; Luloffs, *Rec. Trav. chim.*, 1901, **20**, 292). The replacement of fluorine has received much less attention; nevertheless, in the aromatic

* Part II, preceding paper.

series Holleman (*ibid.*, 1904, **23**, 256) estimated that 1-fluoro-2 : 4-dinitrobenzene reacted some 600 times faster than the corresponding chloro-compound with methoxide ion in methanol. With aromatic amines as reagents, Chapman and Parker (*J.*, 1951, 3301) showed that the ratio for the same compounds was about 100—200. Bevan (*J.*, 1951, 2340), using the *p*-halogenonitrobenzenes and ethoxide ion in ethanol, gave rate constants which lead to the ratio F : Cl : Br : I = 228 : 1 : 0·87 : 0·74. On the other hand, Tronow and Kruger (*J. Russ. Phys. Chem. Soc.*, 1926, **58**, 1270), for reaction of the monohalogenobenzenes with methoxide in methanol, showed the reverse order, but with an extreme range I : F = 35·6 : 1. These may be compared with typical values for aliphatic compounds quoted by Hughes (*Quart. Reviews*, 1951, **5**, 245), *viz.*, F : Cl : Br : I = 10^{-3} : 1 : 30 : 80, a range of 8×10^4. Thus there is a change over between the monohalogenobenzenes and the *p*-halogenonitrobenzenes. In this paper, which deals with the reactions of 1-halogeno-2 : 4-dinitrobenzenes with methoxide or *p*-nitrophenoxide ion in methanol, the order F > Cl > Br > I which is found is regarded as the resultant of two opposing factors—a bond-strength factor leading to I > Br > Cl > F, and an electronegativity factor leading to F > Cl > Br > I, the latter being more important. It follows that a different relative weight can give the different orders found in aliphatic compounds, and halogenonitro- and dinitro-benzenes. The intermediate character of the halogenobenzenes agrees well with this, and they are now being investigated in this laboratory in confirmation.

The unusually high reactivity of aromatic fluoronitro-compounds is also involved in the use of 1-fluoro-2 : 4-dinitrobenzene for forming derivatives of amino-compounds (Sanger, *Biochem. J.*, 1945, **39**, 507) and alcohols (Whalley, *J.*, 1950, 2241). However, Whalley uses triethylamine as catalyst and it is almost certain that the actual reagent is then the 2 : 4-dinitrophenyltriethylammonium ion, the amine being re-formed by the reaction with the alcohol. Rarik, Brewster, and Dains (*J. Amer. Chem. Soc.*, 1933, **55**, 1289) used *p*-fluoronitrobenzene similarly.

In Part I (*loc. cit.*) it is shown, *inter alia*, that the replacement reaction generally will be facilitated by variation of the replaced group (X) as follows. (*a*) An electron-attracting group is able more easily to go off as X^- (the negative sign being relative), and, by rendering the ring carbon atom to which it is attached more positive, facilitates attack by the reagent; within any polar category, the most electronegative atom or group is then most easily replaced: *e.g.*, F > Cl > Br > I. (*b*) The weaker the Ar–X bond the more easily is X replaced. Factors (*a*) and (*b*) are conflicting in the halogens, but the bond-energy factor is not the major one except when (i) the effects due to differences in electronegativity are small, (ii) there is little activation by other groups, and (iii) the nucleophilic power of the reagent is small. This follows because in nucleophilic attack on aromatic systems, it is of prime importance to denude the point of attack of π electrons, and also because the ease of breaking the Ar–X bond is of greater relative importance as the reagent becomes weaker.

The halogens form a particularly suitable group to illustrate these points, since the order of electronegativity is F > Cl > Br > I, and the order of bond strength, with its opposite result, is the same.

In the reactions discussed here: (i) the electronegativity differences are large between fluorine and the other halogens and considerably less between chlorine, bromine, and iodine; (ii) there is powerful activation by other groups, the S.R.F.s (substituent rate factors) of the *o*- and *p*-nitro-groups being 2·17 and $6{\cdot}19 \times 10^5$ at 0° and 1·37 and $4{\cdot}73 \times 10^4$ at 81·6° (preceding paper); (iii) the nucleophilic reagent is a powerful one. This leads to the predicted order F > Cl > Br > I.

The rate constants measured experimentally are shown in Table 1, together with some (shown in parentheses) calculated from them by using the experimental Arrhenius parameters. The activation energies and frequency factors are given in Table 2, and some physical data used in discussion in Table 3.

In Table 3, Ar–Hal bond strengths are for the halogenobenzenes (Landolt–Börnstein, "Tabellen," 6 Auflage, 1 Band, 2 Teil, p. 37). The additional ionic resonance energies were computed by the arithmetic mean method (Pauling, "Nature of the Chemical Bond," 2nd edn., p. 48), by use of halogen molecule bond strengths (*idem, ibid.*, p. 49) and bond

strength Ph–Ph = 102 kcal. (Landolt–Börnstein, *op. cit.*, p. 38). The differences between the computed values are given in the table.

Owing to the much more reactive nature of the fluoro-compound, rate constants for it were measured with sodium *p*-nitrophenoxide. A trial with the *m*-nitrophenoxide showed it to react inconveniently fast.

TABLE 1.

Halogen in 1-halogeno-2 : 4-dinitrobenzene	Temp.	10^3k_2 for reaction with : OMe⁻	*p*-$NO_2{\cdot}C_6H_4{\cdot}O^-$	Ratio (Cl = 1) at : 0°	15°	25°	35°	50°
Fluorine	0·0°	—	(0·631)					
	15·0	—	3·42					
	25·0	—	9·62	2880	2150	1800	1520	1200
	35·0	—	25·3					
	50·0	—	(96·2)					
Chlorine	0·0	2·00	(0·000219)					
	15·0	10·6	(0·00159)					
	18·5	15·3	—					
	22·0	21·9	—	1	1	1	1	1
	25·0	29·6	(0·00535)					
	35·0	(76·7)	(0·0166)					
	50·0	(287)	(0·0799)					
Bromine	0·0	1·38	—					
	15·0	7·10	—					
	20·0	11·8	—	0·690	0·670	0·659	0·640	—
	25·0	19·5	—					
	35·0	(49·1)	—					
Iodine	0·0	(0·308)	—					
	15·0	1·90	—	0·154	0·179	0·195	0·213	—
	25·0	5·76	—					
	35·0	16·3	—					

A preliminary run with the fluoro-compound and sodium *m*-nitrophenoxide gave $k_2 \sim 1 \times 10^{-4}$ at 0°, and no further runs with this reagent were made.

TABLE 2.

Reagent	Arrhenius parameters	Halogen in 1-halogeno-2 : 4-dinitrobenzene : F	Cl	Br	I
OMe^-	E (kcal.)	(14·35)	17·43	17·07	18·97
	$\log_{10} B$	(12·28)	11·26	10·81	11·68
p-$NO_2{\cdot}C_6H_4{\cdot}O^-$	E (kcal.)	17·62	20·70	—	—
	$\log_{10} B$	10·91	9·89	—	—
Probable error in E		±0·02	±0·04	±0·04	±0·11

TABLE 3.

	Halogen in 1-halogeno-2 : 4-nitrobenzene : F	Cl	Br	I
Ar–Hal bond strengths (kcal.)	115	90	76	54
Bond-strength differences	61	36	22	0
Ionic resonance-energy differences (kcal.)	47·3	25·2	17·0	0
Ar–Hal bond lengths (Å)	1·31	1·69	1·88	2·05
Aliph–Hal bond lengths (Å)	1·41	1·76	1·90	2·10
Van der Waals radii (Å)	1·35	1·80	1·95	2·15
Overlaps—planar aromatic compound (Å)	0·32	0·75	0·84	1·00
Overlaps—transition state (Å)	0	0·02	0·12	0·26

To relate fluorine through chlorine to the other compounds, the rates of attack by *p*-nitrophenoxide on the chloro-compound are required. They are given below, and the values of activation energy and frequency factor given in Table 2 are calculated from them. The latter are used to calculate the rate constants at lower temperatures given in Table 1.

Temp.	69·9°	74·2°	81·6°	100·8°
Rate constant (10^4k_2)	5·18	7·22	14·1	64·2

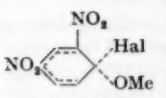
Discussion of Results.—The results show very clearly the order $F \gg Cl > Br > I$; the actual ratios of course vary with temperature owing to differences in activation energy. The latter shows an interesting relationship; there is a marked rise from F to Cl, and a

further smaller rise from Cl and Br to I, but the value for Br is less than that for Cl. The frequency factors are also not in a simple relation, being in the order F > I > Cl > Br.

It is implicit in this discussion that the relationships which hold for the physical constants of the halogenobenzenes also hold for the halogenodinitrobenzenes, even though the absolute values may differ.

The main difference between the Ar–Hal bonds is that the Ar–F bond has much more ionic character than the others, and by rendering the carbon atom to which it is attached more positive it greatly facilitates attack by the reagent. This is shown clearly by the activation energy difference between the F and Cl compounds, *viz.*, 3·08 kcal.

Although the relatively small size of the fluorine atom implies less interference with the conjugation of the *o*-nitro-group and the ring, and thus its activating power (cf. Wheland and Danish, *J. Amer. Chem. Soc.*, 1940, **62**, 1125; Spitzer and Wheland, *ibid.*, p. 2995), yet the transition state may be assumed to have the entering and expelled groups not in the plane of the ring but in a plane at right angles to it, and thus steric effects are very much reduced. This is clearly shown if a model of the transition state of the type is constructed. It should also be noted that in contrast to the S_N2 mechanism in aliphatic compounds, only four groups are bonded in the transition state.



A planar model for the 1-halogeno-2 : 4-dinitrobenzenes can be constructed by using Archer's experimental values (*Proc. Roy. Soc.*, 1947, *A*, **188**, 51) for the ring and the nitro-groups, and Landolt–Börnstein values for the Ar–Hal bond distances. The van der Waals radii of oxygen and the halogens (Pauling, *op. cit.*, p. 189) being used, values are obtained for overlaps (Table 3) which give an indication of the compression and distortion present in these compounds, although the differential effect will be proportional to some power of these overlap distances.

A similar model may be made for the transition state if it is assumed that (i) the six ring carbon atoms are in one plane with the two nitro-groups, (ii) the entering and expelled groups are in a plane at right angles to the ring plane, (iii) the C–O and C–Hal bonds are at 54° 44′ ($\frac{1}{2}$ × tetrahedral angle) to the ring axis, and (iv) the C–O and C–Hal bond distances are those for aliphatic compounds (these would be minimum values). In this model it is found that the fluorine atom is now well clear, and that although the other halogen atoms still have overlaps, these are small, varying from 0·02 Å for Cl to 0·26 Å for I (Table 3). The methoxy-group does not interfere. In view of this, it is assumed that, where only the one *ortho*-group is present, the activation energy is not affected to any important extent. This is confirmed by comparison of *o*- and *p*-chloronitrobenzenes (Part II, preceding paper).

In these reactions the transition state has its charge distributed as compared with the reactants, *i.e.*, there is a loss of solvation energy in forming the transition state. However, (i) the greatest loss of solvation will be where the charge is most distributed, *i.e.*, in the most symmetrical bonding of O and Hal. From Pauling's electronegativity indices (*op. cit.*, p. 64), the asymmetry for F and Cl, relative to O, is similar though in opposite directions, and increases through Br to I. This alone would cause a loss of solvation energy in the order F = Cl > Br > I. On the other hand, (ii) that portion of the charge residing on the halogens causes solvation decreasing in the order F > Cl > Br > I. (iii) Reactions in which the charge does not change in magnitude, but merely in distribution, have comparatively small solvent effects (Hughes and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 657). In view of these factors it is assumed that solvation is unimportant in its differential effect.

The conflicting factors of electronegativity and bond strength are thus left to explain the experimental results, and the data of Table 3 permit a crudely quantitative estimate of their relative importance. If *A* is the difference in ionic resonance energy, *B* the difference in bond strength, and *C* the difference in activation energy (all in kcal.), then the equation $0{\cdot}26B - 0{\cdot}43A = C$ agrees quite well with the experimental values, as shown below :

	Halogen in 1-halogeno-2 : 4-dinitrobenzene :			
	F	Cl	Br	I
C (actual)	−4·62	−1·54	−1·90	0
C (calc.)	−4·48	−1·48	−1·59	0

In particular, the calculated values run parallel to the lowering of activation energy from I to Br, there is a slight rise from Br to Cl, and a considerable drop from Cl to F. An important result is that electronegativity is given about 1·65 times the weight of the bond strength, both being measured as stated above. Even small variations of the coefficients of the equation lead to loss of agreement.

The differences in values of the frequency factor do not lend themselves to such a detailed treatment, but a reasonable explanation of the order F > I > Cl > Br lies in the effect of two opposing factors on the entropies, which are included in the frequency-factor term, *viz.*, the frequency factors (i) decrease in the order F > Cl > Br > I owing to steric retardation of the approach of the anion to the ring carbon atom, and (ii) increase in the order F < Cl < Br < I owing to an increase, in the same order, of release of compression in passing from the initial to the transition states.

Bevan (*loc. cit.*), dealing with a similar group of reactions, regards his discussion as only a tentative one, and does not discuss the variations of activation energies and frequency factors. Chapman and Parker (*loc. cit.*) regard solvation as the main cause of the variation of these terms in their reactions. Hughes and Ingold's theory of solvent action (*loc. cit.*) leads to the conclusion that solvation is much more important in the reactions they studied.

Experimental

The runs were followed as in Part II; but the rate constants were obtained by a graphical method.

Materials.—Fluorobenzene. This was prepared by a standard procedure.

1-*Fluoro*-2 : 4-*dinitrobenzene.* Published procedures gave rather poor yields, but the following method of nitration gave an 80% yield of purified product. Dry fluorobenzene (30 g.) was added dropwise (1 hour) and with mechanical stirring to a mixture of nitric acid (*d* 1·5 ; 76 ml.) and concentrated sulphuric acid (136 ml.), the temperature being kept at 15—20°. The temperature was subsequently raised to 35—40° for an hour, 60—65° for an hour, and finally 80—85° for an hour, vigorous stirring being maintained. The mixture was then cooled and poured into iced water (1 l.). The supernatant liquid was poured off from the precipitated solid, which was washed (molten) with hot water three times and with iced water once. The white substance was dried in a cool vacuum-desiccator (yield 55 g., 96%), and then distilled under reduced pressure through a short column; a fraction, b. p. 163—164°/11 mm., was collected and gave white crystals of 1-fluoro-2 : 4-dinitrobenzene, m. p. 26° (lit., 25·8°).

1-*Chloro*-2 : 4-*dinitrobenzene.* The commercial product, purified by recrystallisation, had m. p. 50·5°.

1-*Bromo*-2 : 4-*dinitrobenzene.* This was prepared from bromobenzene by a procedure similar to that of Dame and Hoffmann (*J. Amer. Chem. Soc.*, 1919, **41**, 1015) for preparing the corresponding chloro-compound. The final product had m. p. 72·5—73°.

1-*Iodo*-2 : 4-*dinitrobenzene.* This was prepared from 2 : 4-dinitroaniline by standard procedures using nitrosylsulphuric acid, followed by aqueous potassium iodide. The final product had m. p. 88·5°.

p-*Nitrophenol.* The commercial product was recrystallised and had m. p. 114·5°.

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680. *The Dielectric Polarisation of Solutions. Part I. The Polarisations and Apparent Dipole Moments of Various Primary, Secondary, and Tertiary Amines in Solutions in Non-polar Solvents and in the Liquid State.*

By Eric G. Cowley.

The polarisations and apparent dipole moments of 18 aliphatic and aromatic amines have been determined in non-polar solvents, and those of 15 liquid amines in the pure state. Further measurements on aniline indicate that, in the majority of solvents, the dipole moment is lower than in the vapour state. In most of the compounds, the effect of the solvent on the moment of the solute is small. *n*-Propyl- and *n*-butyl-amine show larger moments in all the solvents used than in the vapour state. The changes in moment in the corresponding primary, secondary, and tertiary amines are compared. The variation of polarisation with change of concentration from infinitely dilute solution to the pure amine is considered and shown to depend on the type of amine and its dielectric constant. Calculations of the polarisations of the vapours according to Onsager's theory, from the physical constants of the liquid amines, do not give good agreement with experimental values which are available in only a few instances. Small, but definite, changes in the apparent molecular solution volumes of the amines in the different solvents are found and these results are qualitatively discussed.

The objects of this work were the study of the effect of hexane and benzene on the polarisations and apparent moments of amines, the investigation of the changes in moment produced by different alkyl and aryl groups attached to the nitrogen atom, and the comparison of the polarisations of the pure amines with those of the amines in solution at infinite dilution and, where possible, in the vapour state.

The polarisations and apparent dipole moments of aniline in four non-polar solvents at 20° were measured by Cowley and Partington (*J.*, 1938, 1598), who found that the values in benzene and toluene were slightly greater, and those in hexane and *cyclo*hexane were lower, than the moment of the vapour (Groves and Sugden, *J.*, 1937, 1782). The present research (Cowley, *Nature*, 1951, **168**, 705) reports further results for aniline in three other non-polar solvents as well as measurements of the dipole moments of various other amines mainly in hexane and benzene at 20°. Table 1 contains the values of the polarisations of the solutes at infinite dilution, $P_{2\infty}$, the electronic polarisations of the solutes, P_E, measured as the molecular refraction for sodium D light, and the apparent dipole moments, in Debye units, calculated either from $(P_{2\infty} - P_E)$ or from $(P_{2\infty} - P_{E+A})$, where P_{E+A} is taken as $1{\cdot}05\ [R]_D$; both these methods of calculation have been used in the results quoted below. The solvent and its dielectric constant are stated for each measurement and all the values refer to 20·0°.

The Solvent Effect on the Moment of Aniline.—Cowley and Partington (*loc. cit.*) showed that their experimental moments of aniline increased slightly (0·05 D) with the dielectric constants of the four solvents used, but drew no final conclusion regarding the sign of the solvent effect. In the previous work, carbon tetrachloride and carbon disulphide were not at first used as solvents for, on storage, solutions of aniline in these liquids showed evidence of interaction, but later it was found that consistent results could be obtained if measurements were made on freshly prepared solutions. The results obtained, together with that in tetralin, shown in Table 1, indicate a fall in polarisation with an increase in the dielectric constant of the solvent. Thus, apart from the results in benzene and toluene, the dipole moments of aniline in the remaining five solvents are smaller than the moment of the vapour. Since Cowley and Partington's paper, several authors have published work on aniline. Emblem and McDowell (*J.*, 1946, 641) determined the moment (corrected for P_A) in benzene as 1·54 at 20°. Le Fèvre, Roberts, and Smythe (*J.*, 1949, 902) studied the variation of polarisation with concentration of aniline in benzene, and pointed out that it is only for liquid aniline that the electric double refraction is known to be negative, and that the

separate molecules in solution contribute positively to the electric double refraction, as is indicated by Lippmann's results (*Z. Elektrochem.*, 1911, **17**, 15) for benzene–aniline mixtures.

TABLE 1. *Polarisations and apparent moments of various amines at* 20°.

Amine	Solv.	ε	$P_{2\infty}$	P_E	P_{O+A}	μ	P_{E+A}	P_O	$\mu_{corr.}$*
NH_2Pr^n	C_6H_{14}	1·894	59·0	19·4	39·6	1·38	20·4	38·6	1·36
	C_6H_6	2·283	57·3	19·4	37·9	1·35	20·4	36·9	1·33
$NHPr^n_2$	C_6H_{14}	1·894	55·5	33·5	22·0	1·03	35·2	20·3	0·99
	C_6H_6	2·281	57·1	33·5	23·6	1·07	35·2	21·9	1·03
NPr^n_3	C_6H_6	2·283	59·5	47·7	11·8	0·75	50·0	9·5	0·68
NH_2Bu^n	C_6H_{14}	1·895	62·0	24·1	37·9	1·35	25·3	36·7	1·33
	C_6H_{12}	2·019	61·8	24·1	37·7	1·35	25·3	36·5	1·32
	C_6H_6	2·282	64·5	24·1	40·4	1·39	25·3	39·2	1·37
$NHBu^n_2$	C_6H_{14}	1·897	65·8	42·8	23·0	1·05	44·9	20·9	1·00
	C_6H_6	2·276	67·3	42·8	24·5	1·09	44·9	22·4	1·04
cyclo-$C_6H_{11}\cdot NH_2$	C_6H_{14}	1·891	68·7	31·3	37·4	1·34	32·8	35·9	1·31
	C_6H_6	2·280	66·0	31·3	34·7	1·29	32·8	33·2	1·26
$NH_2\cdot CH_2Ph$	C_6H_{14}	1·895	68·8	34·4	34·4	1·29	36·2	32·6	1·25
	C_6H_{12}	2·019	69·6	34·4	35·2	1·30	36·2	33·4	1·27
	C_6H_6	2·280	71·2	34·4	36·8	1·33	36·2	35·0	1·30
	C_7H_8	2·379	66·9	34·4	32·5	1·25	36·2	30·7	1·21
$NH(CH_2Ph)_2$	C_6H_{14}	1·898	87·0	63·6	23·4	1·06	66·7	20·3	0·99
	C_6H_6	2·280	88·0	63·6	24·4	1·08	66·7	21·3	1·01
$N(CH_2Ph)_3$	C_6H_6	2·280	107·0	93·4	13·6	0·81	98·1	8·9	0·65
NH_2Ph	CCl_4	2·236	76·2	30·6	45·6	1·48	32·1	44·1	1·46
	CS_2	2·641	75·0	30·6	44·4	1·46	32·1	42·9	1·44
	$C_{10}H_{12}$	2·757	71·7	30·6	41·1	1·41	32·1	39·6	1·38
$NHPh_2$	C_6H_{14}	1·894	79·7	58·2	21·5	1·02	61·1	18·6	0·95
	C_6H_6	2·280	79·9	58·2	21·7	1·02	61·1	18·8	0·95
NPh_3	C_6H_6	2·283	92·0	83·3	8·7	0·65	87·5	4·5	0·47
NHPhMe	C_6H_{14}	1·884	96·6	35·7	60·9	1·71	37·5	59·1	1·69
	C_6H_6	2·285	93·4	35·7	57·7	1·67	37·5	55·9	1·64
$NPhMe_2$	C_6H_{14}	1·884	92·7	40·7	52·0	1·58	42·8	49·9	1·55
	C_6H_6	2·280	93·5	40·7	52·8	1·59	42·8	50·7	1·56
NHPhEt	C_6H_{14}	1·884	100·2	40·4	59·8	1·70	42·4	57·8	1·67
$NPhEt_2$	C_6H_{14}	1·895	120·8	50·2	70·6	1·84	52·7	68·1	1·81
	C_6H_6	2·276	120·0	50·2	69·8	1·83	52·7	67·3	1·80
NHPhPr^n	C_6H_{14}	1·885	104·8	45·1	59·7	1·69	47·4	57·4	1·66
	C_6H_6	2·285	104·1	45·1	59·0	1·68	47·4	56·7	1·65
NPhEtPr^n	C_6H_{14}	1·895	124·1	54·9	69·2	1·82	57·7	66·4	1·79
	C_6H_6	2·284	125·2	54·9	70·3	1·84	57·7	67·5	1·80

* Corrected for P_A.

Few and Smith (*J.*, 1949, 753) attributed the higher value of the dipole moment of aniline in dioxan than in benzene to hydrogen bonding between the hydrogen of the amino-group and the oxygen atoms of the solvent molecules (cf. Kumler and Halverstadt, *J. Amer. Chem. Soc.*, 1941, **63**, 2182; Wassiliew and Syrkin, *Acta Physicochim. U.R.S.S.*, 1941, **14**, 414). It may be noted that Higasi (*Bull. Inst. Phys. Chem. Res. Tokyo*, 1934, **13**, 1167) found that the dipole moment of aniline in ether is appreciably larger than the values in hexane or benzene. In a further paper, Few and Smith (*J.*, 1949, 3057) measured the dipole moment of aniline in *n*-heptane (1·477), carbon tetrachloride (1·458), and carbon disulphide (1·420) [all results at 25° calculated from $(P_{2\infty} - 1{\cdot}05[R]_D)$]. The results in carbon tetrachloride and carbon disulphide are close to those in Table 1, but Few and Smith used values of the molecular refraction determined in the various solvents, whereas the value for the pure liquid is used here.

Few and Smith (*loc. cit.*, p. 3057) suggest that aniline has a slight negative solvent effect, their values of the moment in solution lying below the vapour result and falling with the dielectric constant of the solvent, and that the value in benzene is slightly higher than expected. This is similar to the conclusion drawn for nitrobenzene that the moment is anomalously high in benzenoid solvents (Smith and Cleverdon, *Trans. Faraday Soc.*, 1949, **45**, 109). Few and Smith calculated the angle between the resultant dipole and the benzene ring in aniline as 53°, allowance being made for the mesomeric effect. This angle is slightly less than that given by Frank's theory (*Proc. Roy. Soc.*, 1935, *A*, **152**, 171), which predicts a negative solvent effect in molecules with a single radical not on the dipole axis when the

angle between the radical and the dipole axis is less than 55° (cf. discussion by Cowley and Partington, *loc. cit.*).

Thus Cowley and Partington (*loc. cit.*) and Cowley (present research) have determined the dipole moment of aniline in seven solvents, and Few and Smith (*loc. cit.*) in five, and in all cases its moment as solute is less than that as vapour, the results in benzene, toluene, and dioxan being excluded. The weight of the evidence, therefore, is that aniline shows the more usual negative solvent effect, the differences, however, being fairly small.

Comparison of Moments of Amines.—The measurements on eight of the amines recorded in Table 1 are new, and there are no earlier values of the dipole moments of any of the compounds (apart from aniline) listed in Table 1 in hexane, *cyclo*hexane, or toluene. The dipole moments of amines investigated by other workers (several after this work was completed) are given with the relevant details in Table 2.

As already pointed out (Cowley, *loc. cit.*), the results of the present research for six amines, *viz.*, *n*-propyl-, *n*-butyl-, and diphenyl-amine, and methyl-, dimethyl-, ethyl-,

TABLE 2. *Published values of molar polarisations and dipole moments of amines.* (All were in benzene solution except those marked * which were as vapour; and all relate to 25° except where noted or where vapour was used.)

Amine	P_∞	$[R]_D$	μ calcd. from :	μ	Ref.
NH_2Pr^n	—	—	slope P–$1/T$ line 8301·7; intercept 23·18	1·17 *	1
	55·9	19·4	32·7	1·26	1
			$P_\infty - [R]_D$	1·34	1
NH_2Bu^n	—	—	slope P–$1/T$ line 6130·72; intercept 34·10	1·00 *	1
	63·7	24·5	29·6	1·20	1
			$P_\infty - [R]_D$	1·38	1
	64·0	24·06	$P_\infty - [R]_D$	1·40	2
	61·13	24·22	$P_\infty - 1{\cdot}05[R]_D$	1·32	3
cyclo-$C_6H_{11}{\cdot}NH_2$	65·7	30·5	$P_\infty - [R]_D$	1·32	4
NHPhMe	93	36	57	1·64	5
	93·20	35·81	55·20	1·643	6
	93·1$_3$	35·68	$P_\infty - [R]_D$	1·67	1
$NPhMe_2$	—	—	$P - 1{\cdot}05[R]_D$	1·61 *	7
	—	—	—	1·39 †	8
	94	41	53	1·58	5
	97·6	46·7 (P_{E+A})	$P_A = 15\%$ of P_E	1·55	9
	94·06	41·17	50·83	1·577	6
	93·6	41·6	$P_\infty - [R]_D$	1·58	10
				1·53 †	11
	94·1$_4$	40·82	$P_\infty - [R]_D$	1·61	1
NHPhEt	100	40	60	1·68 §	12
	99·5$_4$	40·44	$P_\infty - [R]_D$	1·70	1
$NPhEt_2$	108	50·2	$P_\infty - [R]_D$	1·65 †	13
	117·5	50·20	$P_\infty - [R]_D$	1·81	1
$NHPh_2$	93·7	58·4 (P_{solid})	35·3	1·3 §	14
	79·8	57·3	22·5	1·04	15
	81·22	57·3	$P_\infty - [R]_D$	1·08	16
	79·0	57·6	$P_\infty - [R]_D$	1·0	1
NPh_3	—	—	$P_\infty - P_E = 1{\cdot}43$ ($P_A = 0$)	0·26 ‡	17
				0·71	18

† See notes in relevant references. § At 20°. ‡ At 15°.

References : (1) Barclay, Le Fèvre, and Smythe, *Trans. Faraday Soc.*, 1951, **47**, 357. (2) Rogers, *J. Amer. Chem. Soc.*, 1947, **69**, 457. (3) Few and Smith, *J.*, 1949, 2663. (4) Lewis and Smyth, *J. Amer. Chem. Soc.*, 1939, **61**, 3067. (5) Fogelburg and Williams, *Physikal. Z.*, 1931, **32**, 27 : recalculation of μ gives 1·67 for methylaniline and 1·61 for dimethylaniline. (6) Few and Smith, *J.*, 1949, 753 : μ calculated from $P_\infty - 1{\cdot}05[R]_D$. (7) Groves and Sugden, *J.*, 1937, 1782. (8) Højendahl, *Nature*, 1926, **117**, 892 : method of calculation and temp. not stated. (9) Hertel and Dumont, *Z. physikal. Chem.*, 1935, *B*, **30**, 139. (10) Marsden and Sutton, *J.*, 1936, 599. (11) Fischer, *Nature*, 1950, **165**, 239 : solvent, temp., and method of calculation not stated. (12) Cowley and Partington, *J.*, 1933, 1257. (13) Krasilnikov, *J. Phys. Chem., U.S.S.R.*, 1944, **18**, 174 : temp. apparently 20°. (14) Estermann, *Z. physikal. Chem.*, 1928, *B*, **1**, 134. (15) Leonard and Sutton, *J. Amer. Chem. Soc.*, 1948, **70**, 1565 : μ 0·99 with $P_A = 5\%$ of P_E. (16) Smith, *J.*, 1950, 3532 : μ 1·016 from $P_\infty - 1{\cdot}05[R]_D$. (17) Bergmann and Schütz, *Z. physikal. Chem.*, 1932, *B*, **19**, 401. (18) Warburton, result quoted by Leonard and Sutton (ref. 15) : μ 0·55 with $P_A = 5\%$ of P_E.

and diethyl-aniline in benzene at 20° are in close agreement with those of Barclay, Le Fèvre, and Smythe (*loc. cit.*) in the same solvent at 25°, the comparison being made between the dipole moments calculated with the same assumptions regarding the distortion polarisation. The latter authors' value of $[R]_D$ of *n*-butylamine is slightly higher than the present value, which confirms that of Rogers (*loc. cit.*): when the present value of the molecular refraction is used, their moment is identical with the result now reported (1·39). All these results for *n*-butylamine are slightly higher than that of Few and Smith (*loc. cit.*), *viz.*, 1·34 in benzene at 25°, if calculated from $P_\infty - [R]_D$. The difference between the moments of *cyclo*hexylamine in benzene reported here and that of Lewis and Smyth (*loc. cit.*) is also due to use of different values of molecular refraction, the present value agreeing closely with Vogel's result (*J.*, 1948, 1825). Recalculation of Lewis and Smyth's result using this figure gives 1·30, compared with 1·29 (Table 1).

The moment of methylaniline found here and by Le Fèvre *et al.* (*loc. cit.*) is slightly greater than that found by Few and Smith (*loc. cit.*), and our value for dimethylaniline agrees with three of the earlier published results. Barclay, Le Fèvre, and Smythe's value for ethylaniline is close to that of Cowley and Partington (*loc. cit.*), but the former authors' result for diethylaniline, now confirmed, is considerably greater than that of Krasilnikov (*loc. cit.*). For diethylaniline the latter worker found a variation of polarisation with concentration from infinite dilution to the pure amine of the shape found for some alcohols, and this is different from the results now reported for benzene and hexane solutions over the range of mole-fraction from zero to 0·04. Krasilnikov's result may be explained by the fact that the dielectric constants are given to only three significant figures, which would greatly affect the results for dilute solutions. The present values of the moment of di- and tri-phenylamine are in satisfactory agreement with the other results.

Variation of Moment of Amines.—The results show that the change of moment from *n*-propyl- to *n*-butyl-amine is small, the moments of benzyl- and *cyclo*hexyl-amine being a little lower than the mean of the values for the other compounds. Smyth (*J. Amer. Chem. Soc.*, 1924, **46**, 2151) calculated the moments of benzyl- and dibenzyl-amine as approximately 1·14 and 1·15, which the experimental figures now show to be of the right order. The branched-chain primary butylamines have lower moments than *n*-butylamine, *viz.*, *iso*- 1·27 (Barclay, Le Fèvre, and Smythe, *loc. cit.*), *sec.*- 1·28, *tert.*- 1·29 (Rogers, *loc. cit.*), and 1·34 (Few and Smith, *J.*, 1949, 2663); all values relate to benzene solution at 25° and are calculated from the difference $(P_\infty - [R]_D)$.

TABLE 3. *Change in dipole moment from primary to secondary to tertiary amine in benzene solution.*

Group or groups (R) in amine		μ of primary amine	Difference in μ: $NH_2R - NHR_2$	$NHR_2 - NR_3$
Me		1·46	0·29	0·31
Et		1·28	0·25	0·11
Pr^n		1·35	0·28	0·32
Bu^n		1·39	0·30	—
CH_2Ph		1·33	0·25	0·27
Ph		1·53	0·51	0·37
	Anilines: methyl		−0·14	0·08
	ethyl		−0·15	−0·15
	n-propyl		−0·15	−0·16 *

* Difference between moments for *n*-propyl- and ethyl-*n*-propyl-aniline.

The changes in moment produced as the hydrogen atoms of the primary amine group are successively replaced by further alkyl or aryl groups are given in Table 3, all the data referring to results in benzene solution. (The values of the moments determined in hexane show approximately the same variation.) The values are those of the present research, except those for the methylamines (Le Fèvre and Russell, *Trans. Faraday Soc.*, 1947, **43**, 374), the ethylamines (Barclay, Le Fèvre, and Smythe, *ibid.*, 1950, **46**, 812; Le Fèvre, *ibid.*, 1952, **48**, 580), and aniline (Cowley and Partington, *loc. cit.*).

In the alkylamines, an approximately constant difference exists between the moments of the corresponding primary and secondary amines and also between the corresponding secondary and tertiary amines, with the exception of the smaller differences found between

the ethylamines. The differences between the benzylamines are slightly smaller than those in the alkylamines, but in the series aniline, diphenylamine, triphenylamine the differences in moment are larger, that between the first two being much greater than that between the last two. In the replacement of the remaining hydrogen of the imino-group, the change from methyl- to dimethyl-aniline produces a small decrease in moment, but replacement by an ethyl group in either ethyl- or *n*-propyl-aniline causes in both cases the same increase in moment, *viz.*, 0·15.

The angles between the groups in these compounds are not available from direct measurements except for trimethylamine, where the C–N–C angle is 108°±4° (Brockway and Jenkins, *J. Amer. Chem. Soc.*, 1936, **58**, 2036). Leonard and Sutton (*loc. cit.*) have calculated this angle in di- and tri-phenylamine as 113° and 114°, respectively, from the dipole moments of the amines, the *p*-substituted fluoro-derivatives of these amines, and fluorobenzene. They regard the differences between these angles and that in trimethylamine as real and as indicating resonance with structures involving the grouping $=\overset{+}{\mathrm{N}}<$, although neither amine is coplanar. Similarly, the difference in moment of the amino-group in the aliphatic and aromatic series is usually attributed to the mesomeric effect of the amino-group, which gives rise to the resonance.

Polarisations of Amines as Vapours or Liquids.—Of the compounds now used, only *n*-propylamine, *n*-butylamine, and dimethylaniline have been investigated in the vapour state, the polarisation then being lower for the first two, but higher for the last, than the corresponding solution results, as shown in Table 4. The moments of *n*-propylamine and

TABLE 4. *Total polarisation of amines in the vapour state and in solution at* 20°.

Amine	$\mu_{vap.}$	Total polarisation: Vapour	In C_6H_{14}	In C_6H_{12}	In C_6H_6 [1]
n-Propylamine	1·17	51·7 [2]	59·0	—	57·3
n-Butylamine	1·00	50·4 [2]	62·0	61·8	64·5
Dimethylaniline	1·61	96·7 [3]	92·7	—	93·5

[1] All solution results from present research. [2] Calculated from the results of Barclay, Le Fèvre, and Smythe (*Trans. Faraday Soc.*, 1951, **47**, 357). [3] Calculated from the results of Groves and Sugden (*loc. cit.*).

n-butylamine are compared in Table 5 with the apparent moments of the pure liquids, calculated from the difference of the polarisation of the liquid and the molecular refraction (see Table 6), and with the earlier results for methyl- and ethyl-amine.

TABLE 5. *Dipole moments of aliphatic amines.*

Amine	Condition	Mono-	Di-	Tri-	Amine	Condition	Mono-	Di-	Tri-
Me [1]	Gas	1·28	1·02	0·64	Et [3]	Gas	1·22 [5]	0·92 [5]	0·66 [5]
	C_6H_6 soln.	1·46	1·17	0·86		C_6H_6 soln.	1·28 [5]	1·02 [5]	0·91 [5]
	Liquid	1·08	1·13	0·72		Liquid	1·09	1·11	0·75 [5]
Pr^n	Gas	1·17 [4] (1·25)	—	—	Bu^n [3]	Gas	1·00 [4] (1·12)	—	—
	C_6H_{14} soln.	1·38	1·03	—		C_6H_{14} soln.	1·35	1·05	—
	C_6H_6 soln.	1·35	1·07	0·75		C_6H_6 soln.	1·39	1·09	—
	Liquid	1·18	1·04	0·67		Liquid	1·23	1·10	—

[1] Le Fèvre and Russell, *loc. cit.* [2] Barclay, Le Fèvre, and Smythe, *Trans. Faraday Soc.*, 1950, **46**, 812. [3] Present research. [4] Ref. 2, Table 4: μ's calculated from slope of P–$1/T$ line; the figures in parentheses have been calculated from the total polarisation of the vapour $-[R]_D$. [5] Le Fèvre, *ibid.*, 1952, **48**, 580.

The apparent moment of pure liquid *n*-propylamine is lower than that for the vapour or solution, thus resembling the values for methyl- and ethyl-amine, while that of *n*-butylamine lies between the moments of the vapour and that found from solutions. The apparent moments of pure liquid di-*n*-propyl- and di-*n*-butyl-amine are little different from the values found in hexane and benzene, and the difference in apparent moments of tri-*n*-propylamine is relatively small.

Table 6 gives the polarisations and apparent moments of all the liquid amines used in this work. The polarisations of the liquids have been calculated from the dielectric constants and densities at 20° of the pure materials (see Table 10) by the Clausius–Mossotti equation, and the apparent moments by the Debye equation.

TABLE 6. *Polarisations and apparent dipole moments of liquid amines, at 20°.*

Amine	$P_{liq.}$	P_{O+A}*	μ	P_O*	$\mu_{corr.}$†	Amine	$P_{liq.}$	P_{O+A}*	μ	P_O*	$\mu_{corr.}$†
NH_2Pr^n	48·6	29·2	1·18	28·2	1·16	NH_2Ph	61·0	30·4	1·21	28·9	1·18
$NHPr^n_2$	55·9	22·4	1·04	20·7	1·00	NHPhMe	67·7	32·0	1·24	30·2	1·21
NPr^n_3	57·1	9·4	0·67	7·1	0·58	$NPhMe_2$	72·5	31·8	1·24	29·8	1·20
NH_2Bu^n	55·8	31·7	1·23	30·5	1·21	NHPhEt	78·1	37·7	1·35	35·7	1·31
$NHBu^n_2$	68·0	25·2	1·10	23·1	1·05	$NPhEt_2$	93·1	42·9	1·44	40·4	1·39
cyclo-C_6H_{11}·NH_2	63·4	32·1	1·24	30·6	1·21	NHPhPr^n	85·8	40·6	1·40	38·4	1·36
NH_2·CH_2Ph ...	63·5	29·1	1·18	27·3	1·14	NPhEtPr^n.....	99·9	44·9	1·47	42·2	1·42
$NH(CH_2Ph)_2$ ...	86·3	22·7	1·04	19·6	0·97						

* $P_{O+A} = P_{liquid} - P_E$; $P_O = P_{liquid} - P_{E+A}$: for values of P_E and P_{E+A} see Table 1.
† See footnotes to Table 1.

Comparison of results for the pure liquids and for the same amines as solutes shows that the apparent moments of the liquids (Table 6) exhibit a variation similar to that found at infinite dilution in the non-polar solvents (Table 1). It is noteworthy that for the secondary aliphatic or benzyl amines, the moments are very close, but for the other compounds the apparent moments of the liquids are smaller. These amines can be grouped according to the difference between the polarisation at infinite dilution in solution and that of the pure liquid, which is mainly determined by the structure and the dielectric constant of the amine. This difference is very small if the dielectric constant of the secondary amine is 2—3·5; but it is 5—9 c.c. for primary aliphatic amines, benzylamine, and *cyclo*hexylamine, where the dielectric constant is approximately 5; and for the aromatic amines, it is 20—25 c.c. when the dielectric constant is equal to or greater than 5.

Association of Amines.—Attempts to obtain evidence of association in the liquid from the variation of polarisation with change of concentration of the solute in a non-polar solvent have been made, *e.g.*, by Smyth ("Dielectric Constant and Molecular Structure," The Chemical Catalog Company, New York, 1931, ch. 9, p. 169). Davy and Sidgwick (*J.*, 1933, 281) investigated the association of nitrobenzene in benzene and *cyclo*hexane by comparing the change of polarisation in these solvents with the molecular weights determined cryoscopically; since the association did not obey the law of mass action, they concluded that there is no chemical combination between the solute molecules, the fall in activity and polarisation being explained by orientation of the polar molecules under the influence of their mutual attractions.

It is improbable, therefore, that the cause of the fall of polarisation which occurs in "normal" liquids, like nitrobenzene, is chemical association. Van Arkel and Snoek (*Trans. Faraday Soc.*, 1934, **30**, 707) showed that the variation of polarisation with concentration was expressed by the formula

$$\frac{\varepsilon - 1}{\varepsilon + 2} = \frac{4}{3}\pi n\left[\alpha + \frac{\mu^2}{3kT + Cn\mu^2}\right]$$

The constant C was usually independent of n, the number of molecules per c.c., of the nature of the solvent, and largely of the solute molecule, but, in some cases, it varied with concentration and had abnomal values (*e.g.*, with alcohols). It was shown that in many cases C was between 1 and 2, but the amines formed one of several groups of substances which did not obey the equation.

The distinction between dipole association and chemical association is stressed by Wilson (*Chem. Reviews*, 1939, **25**, 377). The dipole association is divided into two classes: co-association, in which dipoles are oriented head to tail so that the dipole moments reinforce each other, and contra-association in which dipoles tend to be oriented in antiparallel configurations, so that the moments cancel each other. Wilson showed that for a few simple molecules it is possible to decide on the type of association from considerations of potential energy.

The changes in polarisation of these amines with concentration are mentioned above. It is found that in every case the polarisation either falls or remains practically unchanged, but it is only in the aromatic series that there is an appreciable fall. It follows that, apart from the latter group, the effect of dipole association is slight.

Other evidence regarding association in these amines is sparse. Turner and Merry

(*J.*, 1910, **97**, 2069) concluded, from a study of the propyl-, amyl-, and benzyl-amines, that the primary amines were slightly associated, and the secondary and tertiary amines non-associated, in the liquid state, and this was confirmed for amyl- and benzyl-amines by molecular-weight determinations in benzene (cf. Turner, "Molecular Association," Longmans, Green and Co., London, 1915, p. 61). The value of Ramsay and Shields's constant increased in the order primary to secondary to tertiary propyl- or benzyl-amine, but since the molecular surface energies of various secondary and tertiary amines were proportional to the temperature, it was concluded that Ramsay and Shields's formula was not valid in these cases. Mussell, Thole, and Dunstan (*J.*, 1912, **101**, 1008), who showed that the ratio of viscosity to molar volume had high values for associated liquids, concluded that the primary amines had the highest ratio for the aliphatic amines. There was a large increase over these values in passing to the aromatic series, although the order primary, secondary, tertiary amine was preserved. Whereas aniline was regarded as associated, benzylamine was normal.

Theoretical Calculation of the Moments of Vapours of Amines.—The experimental moments and those calculated from Onsager's equation (*J. Amer. Chem. Soc.*, 1936, **58**, 1486) are compared in Table 7. The equation may be written

$$P_0 \text{ (vapour)} = \frac{(\varepsilon - n_\infty{}^2)(2\varepsilon + n_\infty{}^2)}{\varepsilon(n_\infty{}^2 + 2)^2} \cdot \frac{M}{d}$$

where ε is the dielectric constant of the pure liquid, n_∞ the refractive index for infinite wave-length, M the molecular weight, and d the density of the liquid. The equation has been tested by Böttcher (*Physica*, 1939, **6**, 59) and in many cases the calculated moments of the vapours are in reasonable agreement with the experimental values. Onsager's expression has been criticised by Wilson (*loc. cit.*) because of the assumed spherical shape of the solute molecule with a central dipole, the treatment of the molecule as a homogeneous continuum, and the arbitrary choice of the cavity used in the deduction: the reaction field, which arises from the polarisation of molecules close to the central dipole, will thus be in error. Wilson deduced a modified equation, which takes account of the optical anisotropy of the polar molecule, and the calculations made from it are in closer agreement with the vapour values than are Böttcher's results.

As the necessary constants for the application of Wilson's equation are lacking, the calculations are now made by means of Onsager's equation. The refractive index for infinite wave-length is obtained from the molecular refraction for the *C* and the *G'* line given by Vogel (*loc. cit.*), by using the formula

$$R_\infty = (\lambda_2{}^2 - \lambda_1{}^2)/(\lambda_2{}^2/R_2 - \lambda_1{}^2/R_1)$$

where R_1 and R_2 are the molecular refractions for the wave-lengths λ_1 and λ_2. The dielectric constants used are recorded in Table 10. The results from Onsager's equation are also compared with values calculated from Wyman's equation (*J. Amer. Chem. Soc.*, 1936, **58**, 1482), *viz.*, P_0 (total polarisation of the vapour) $= M(\varepsilon + 1)/8{\cdot}5d$, where ε and d refer to the pure liquid. This is in accordance with Onsager's equation for high values of the dielectric constant.

The calculated values can be compared with the experimental values of the orientation polarisation of the vapour in only four cases, *viz.*, *n*-propylamine 28·5, *n*-butylamine 20·8, dimethylaniline 53·9, and aniline 46·3 (values at 20° of P_0 in c.c.). The two sets of figures are not in good agreement, all the calculated values being too large. It is found, however, that the values given by the Onsager and the Wyman equation in some cases are quite close to each other and in the *N*-substituted anilines are little different from the values found in the non-polar solvents. No general conclusion regarding the applicability of Onsager's equation to these amines can be drawn in the absence of determinations for the vapours. Le Fèvre *et al.* have found that the moments calculated from Onsager's equation do not give good agreement for the methyl- and ethyl-amines and that the calculated values are too large, as is found here for *n*-propyl- and *n*-butyl-amine. They applied Barclay and Le Fèvre's expression (*J.*, 1950, 556) to some of the aliphatic amines.

The other theoretical solvent-effect equations (see, *e.g.*, Cowley and Partington,

TABLE 7. *Comparison of experimental values of P_O and μ from hexane and benzene solutions with values calculated from Onsager's and Wyman's equations.*

				P_0, c.c.				μ calc. from P_0 for			
				calc. from equation :		found in :		vapour		solution	
Amine	$k_\infty^{20°}$	$n_\infty^{20°}$	ε	Onsager	Wyman	C_6H_{14}	C_6H_6	Onsager	Wyman	C_6H_{14}	C_6H_6
NH_2Pr^n	19·00	1·378	5·31	43·6	40·8	38·6	36·9	1·45	1·40	1·36	1·33
NH_2Bu^n	23·41	1·391	4·88	45·0	43·0	36·7	39·2	1·47	1·44	1·33	1·37
$NHPr^n_2$	32·75	1·395	3·068	26·0	30·2	20·3	21·9	1·12	1·21	0·99	1·03
$NHBu^n_2$	41·82	1·407	2·998	29·1	35·1	20·9	22·4	1·18	1·30	1·00	1·04
NPr^n_3	46·52	1·406	2·277	10·4	23·1	—	9·5	0·71	1·05	—	0·68
cyclo-$C_6H_{11}\cdot NH_2$	30·55	1·447	4·73	43·9	44·2	35·9	33·2	1·45	1·46	1·31	1·26
$NH_2\cdot CH_2Ph$ ...	33·17	1·520	5·18	41·3	43·1	32·6	35·0	1·41	1·44	1·25	1·30
$NH(CH_2Ph)_2$ ...	—	1·565 [1]	3·446	26·2	33·8	20·3	21·3	1·12	1·28	0·99	1·01
NH_2Ph	29·09	1·551	7·07	51·2	53·4	44·9 [3]	47·9 [3]	1·57	1·63	1·47 [3]	1·52 [3]
NHPhMe	33·88	1·536	5·96	49·2	51·4	59·1	55·9	1·54	1·57	1·69	1·64
NHPhEt	38·50	1·522	5·87	57·7	59·7	57·8	58 [2]	1·67	1·69	1·67	1·66 [2]
$NHPhPr^n$	43·08	1·512	5·48	60·2	61·9	57·4	56·7	1·70	1·72	1·66	1·65
$NPhMe_2$	38·74	1·524	5·02	45·0	46·9	49·9	50·7	1·47	1·50	1·55	1·56
$NPhEt_2$	47·80	1·511	5·20	59·0	63·6	68·1	67·3	1·68	1·75	1·81	1·80
$NPhEtPr^n$	—	1·505 [1]	4·90	63·0	64·9	66·4	67·5	1·74	1·77	1·79	1·80

[1] Estimated value. [2] Cowley and Partington, *J.*, 1933, 1257. [3] *Idem*, *J.*, 1938, 1598.

J., 1936, 1184; 1937, 186) cannot yet be applied to the amines as the necessary constants are not available.

Molecular Solution Volumes of Amines.—The density data recorded in the Experimental section have been used to calculate the apparent molecular solution volumes of the amines at 20° (Table 8). The relationship, $V_{12} = V_1x_1 + V_2x_2$, where V is the molar volume and x the mole-fraction and the suffixes 1, 2, and 12 refer to solvent, solute, and solution, respectively, is assumed, and so any volume change is included in the molecular solution volume of the solute. The molar volumes of the pure liquids are calculated from the molecular weights and the densities at 20°.

It is found that the apparent molecular volumes of the aliphatic amines in hexane or benzene are greater than those of the pure liquids. The apparent molecular solution volumes of the *N*-alkyl-substituted anilines and dibenzylamine are smaller than the molar volumes of the liquids, with the exception of the values for diethyl- and ethyl-*n*-propylaniline, which are slightly larger in benzene. For *cyclo*hexylamine and benzylamine the values in hexane are smaller than those in benzene, the molar volumes of the liquids lying between them. Few and Smith (*J.*, 1949, 753) note that the apparent specific volumes of aniline, methylaniline, and dimethylaniline in benzene are lower than the specific volumes of the pure liquids. With the exception of some aliphatic amines, the apparent molecular solution volume is generally greater in benzene than in hexane. The molar volumes of the amines and the values of the atomic volume of nitrogen, deduced from them, are considered in detail by Le Bas ("The Molecular Volumes of Liquid Chemical Compounds," Longmans, Green and Co., London, 1915, p. 197).

Many attempts have been made to correlate volume changes on mixing with the properties of the constituents of the mixture. It has long been recognised that the compressibility and internal pressure are factors influencing volume changes on mixing liquids (*e.g.*, Dawson, *J.*, 1910, **97**, 1896). Tyrer (*ibid.*, p. 2620) placed solvents in order with respect to the magnitude of volume change of the solute, and found that the product of the compressibility and molar volume for the solutes gave the same order as the variation of the specific volume of the solute. The forces of attraction between the solute and solvent molecules were considered to be nearly constant for the substances examined.

Meares (*Trans. Faraday Soc.*, 1949, **45**, 966) studied the volume changes on mixing esters, and analysed the results with respect to the contributing effects. He showed that changes both in geometrical arrangement and in intermolecular forces may occur, and that these effects often act in opposition in their contributions to the resulting volume change. If a geometrical arrangement of molecules occurs, the volume change results from modification of the number of nearest neighbour contacts. This is more likely with molecules of different diameters. Similarly, the nature of the chemical groups in the

TABLE 8. *Apparent molecular solution volumes of amines at 20°.*

Amine	Molar vol. of pure amine	Molecular solution vol. in: C_6H_{14}	C_6H_{12}	C_6H_6	C_7H_8
NH_2Pr^n	82·42	87·6	—	83·7	—
NH_2Bu^n	98·94	100·6	103·8	100·4	—
$NHPr^n_2$	136·97	137·8	—	137·5	—
$NHBu^n_2$	170·04	170·4	—	171·8	—
NPr^n_3	189·33	—	—	192·2	—
cyclo-$C_6H_{11}\cdot NH_2$	114·42	114·4	—	115·4	—
$PhCH_2\cdot NH_2$	109·14	107·6	115·4	109·2	109·9
$NH(CH_2Ph)_2$	192·12	189·0	—	191·6	—
NH_2Ph *	91·15	90·2	96·5	90·4	92·1
NHPhMe	108·64	106·7	—	108·1	—
NHPhEt	126·16	124·9	—	—	—
$NHPhPr^n$	143·10	140·9	—	141·1	—
$NPhMe_2$	126·74	126·2	—	126·7	—
$NPhEt_2$	159·68	157·2	—	160·2	—
$NPhEtPr^n$	176·67	171·8	—	177·3	—
Molar vol. of solvent		128·4	108·2	89·0	106·4

* The molecular solution volume of aniline in carbon tetrachloride is 89·7 (96·5), carbon in disulphide 93·9 (60·2), and in tetralin 91·6 c.c. (136·5), the molar volumes of the corresponding solvents being given in parentheses.

molecules determines the attractive force between the molecules, and so the volume occupied by the mixture may be different from the sum of the separate volumes. The intermolecular energies fall rapidly with distance, so the attractive force is localised in the few atoms in contact on the molecular surfaces. Meares applied Scatchard's theory (*ibid.*, 1937, **33**, 160) to the change of volume, due to modification of geometrical arrangement, of compressibility, and of intermolecular forces, with alteration in the relative amounts of the constituents.

The compressibilities of only a few of the amines used here are available. These figures have been used in the calculation of the internal pressures (P_i) of the liquids (Table 9), where $P_i = T\alpha/\kappa$ in atm. at 293° K.

TABLE 9. *Compressibilities* (κ), *coefficients of expansion* (α), *and internal pressures of some amines and solvents at* 20°.

Compound	$10^6\kappa$ per atm.[1]	Press. range (unit: 10^6 dynes)	$10^4\alpha$ [2]	P_i	Compound	$10^6\kappa$ per atm.[1]	Press. range (unit: 10^6 dynes)	$10^4\alpha$ [2]	P_i
NH_2Ph	4·51	1—9	8·46	4370	C_6H_{14}	1·05	100—500	13·19	3670
NHPhMe ...	4·36	100—500	8·19	5510	*cyclo*-C_6H_{12}	9·42	100—200	11·64	3620
NHPhEt ...	4·76	100—500	8·74	5370	C_6H_6	7·29	100—500	12·12	4870
$NPhMe_2$ ...	4·86	100—500	8·56	5160	PhMe.....	6·99	100—500	10·67	4470
$NPhEt_2$ ...	5·17	100—500	8·45	4790					

[1] I.C.T., 1928, **3**, 35. [2] Results calculated from density–temperature data (*ibid.*, p. 27); ethylaniline from Vogel's results (*J.*, 1948, 1832).

The internal pressures of liquids calculated from the above expression usually give values of 2000—8000 atm. (Hildebrand and Scott, "The Solubility of Non-Electrolytes," Reinhold Publ. Corp., New York, 3rd edn., 1950, p. 96). It is necessary to use in comparisons values determined between the same pressure limits, since the compressibilites vary considerably with differences in pressure ranges. The compressibilites and internal pressures of these *N*-alkylanilines differ more from the values for hexane than from those for benzene, and the greater change of molecular solution volume from that of the corresponding pure amine is found in the hexane solution values.

The effects of the sizes and shapes of the molecules in the mixture must also be considered. Clausius's expression (see Debye, "Polar Molecules," The Chemical Catalog Company, 1929, p. 15) gives the volume occupied by the spherical molecules in the gram-molecular volume as equal to the molecular refraction of the compound. Although the assumption of spherical shape is an approximation, molecules of unassociated liquids at temperatures not near to their freezing points may usually be regarded as occupying spherical volumes, since in the absence of strongly localised fields the molecules can probably rotate freely (Meares, *loc. cit.*). The ratio of molecular refraction to molar

volume will give, therefore, the fraction of the molar volume actually occupied by the molecules. For the amines used here, this fraction, calculated from $[R]_D$/(molar volume of liquid at 20°), has the values: aliphatic amines, 0·24—0·25; *N*-alkylanilines, 0·31—0·33; *cyclo*hexylamine, 0·27; and the benzylamines, 0·31—0·33. The corresponding values for hexane and benzene are 0·23 and 0·30, respectively. The fractions for the aromatic amines are closer to that for benzene than the value for hexane, and the greater free space in the latter solvent might lead to the expectation of a larger decrease in molecular solution volume of the aniline in hexane, as is found. The order here is the same as is found for the internal pressures. The range of concentration used in these solutions is comparatively small, and in most mixtures the variation of molecular solution volume with concentration is no larger than the probable error in the calculations.

Experimental

Measurement of Dielectric Constants.—Some of the determinations were made with the apparatus used by Cowley and Partington (*J.*, 1935, 604; 1936, 1184); the others were made with a redesigned heterodyne-beat apparatus, operating at 1870 kc. The standard condenser was a Muirhead variable air-condenser, with an N.P.L. calibration over the whole scale. The error on the dielectric constants is not more than a few parts per 10,000. The figures have been recorded to three places of decimals and therefore the possible error does not affect these values of the dielectric constant. The higher dielectric constants of some of the pure amines are evidently less accurate and are given to two places of decimals. A check of these results was made by using purified samples of liquids of known dielectric constants and of approximately the same magnitudes as that of the liquid being investigated.

The previously described dielectric cells were used. Some of the measurements were made with a glass dielectric cell with concentric silvered surfaces, fitted with tubes, closed with glass caps, for filling the annular space in the cell. The platinum leads, sealed through glass supporting tubes, made contact with mercury cups on the dielectric-constant apparatus. The cell could also be used for density determinations and it was calibrated with specially purified benzene.

Purification of Materials.—Amines. The amines, of the purest grade obtainable, were all purified carefully before use. The liquid amines were dried (KOH) and repeatedly fractionated. The purified aliphatic amines, *cyclo*hexylamine, benzylamine, and dibenzylamine, were distilled into the solution vessels in a Brühl receiver, so that there was no possibility of contact with atmospheric moisture or carbon dioxide. The *N*-substituted anilines were fractionated several

Table 10. *Physical constants of amines used.*

Amine	B. p./mm.	d_4^{20}	n_D^{20}	ε^{20}	$[R]_D^{20}$, c.c.	$P_{liq.}$, c.c.
NH_2Pr^n	47·0—47·8°/747	0·7172	1·3872	5·31	19·42	48·6
$NHPr^n_2$	109·0—109·5/756	0·7387	1·4045	3·068	33·53	55·9
NPr^n_3	156·5—157·2/764	0·7567	1·4178	2·277	47·65	57·1
NH_2Bu^n	77·0—77·4/762	0·7392	1·4014	4·88	24·06	55·8
$NHBu^n_2$	159·5/770	0·7601	1·4176	2·998	42·78	68·0
cyclo-$C_6H_{11}\cdot NH_2$	134·5—134·6/767	0·8668	1·4592	4·73	31·28	63·4
$NH_2\cdot CH_2Ph$	81·0/20	0·9818	1·5439	5·18	34·45	63·5
$NH(CH_2Ph)_2$	174·0—175·0°/6	1·0270	1·5757	3·446	63·56	86·3
$N(CH_2Ph)_3$	92·0 *	—	—	—	93·4	—
NH_2Ph	76·0/12	1·0220	1·5856	7·07	30·57	61·0
$NHPh_2$	53·0 *	—	—	—	58·2	—
NPh_3	127·0 *	—	—	—	83·3	—
NHPhMe	78·2—78·3/5	0·9863	1·5708	5·96	35·68	67·7
$NPhMe_2$	70·0/3	0·9561	1·5574	5·02	40·73	72·5
NHPhEt	94·8—95·0/6	0·9606	1·5540	5·87	40·43	78·1
$NPhEt_2$	90·7/3	0·9346	1·5414	5·20	50·21	93·1
$NHPhPr^n$	99·6—100·0/4	0·9443	1·5428	5·48	45·11	85·8
$NPhEtPr^n$	122·0—123·0/11	0·9240	1·5340	4·90	54·91	99·9

* M. p.s.

times under reduced pressure and were colourless when used. The solid amines were recrystallised until their m. p.s were constant. Absolute alcohol was the solvent for crystallisation of tribenzylamine and triphenylamine, and light petroleum for diphenylamine. The physical constants of the amines are given in Table 10: they may be compared with the following determinations:

Amines: *n*-propyl, b. p. 48°/750 mm., d_4^{20} 0·7173, n_D^{20} 1·38815;[1] di-*n*-propyl, b. p. 108°/751 mm., d_4^{20} 0·7400,[1] 0·7390,[2] n_D^{20} 1·40499,[1] ε at 22° 2·90;[3] tri-*n*-propyl, b. p.

156·5°/760 mm., d_4^{20} 0·7558,[1] 0·7567,[4] n_D^{20} 1·41760;[1] *n*-butyl, b. p. 77°/750 mm., d_4^{20} 0·7414, n_D^{20} 1·40086,[1] ε at 21° 5·3;[3] di-*n*-butyl, b. p. 159°/761 mm., d_4^{20} 0·7601, n_D^{20} 1·41766;[1] *cyclo*hexyl, b. p. 133°/756 mm., d_4^{20} 0·8671, n_D^{20} 1·45926;[1] benzyl, b. p. 185°/767 mm., d_4^{20} 0·9816, n_D^{20} 1·5438,[1] ε at 20·6° 4·6,[5] at 19·4° 5·2;[6] dibenzyl, b. p. 177·5—178·0°/16 mm., d_4^{20} 1·0272,[4] 1·0276,[2] $n_D^{21\cdot6}$ 1·57432,[4] ε at 20° 3·55,[3] at 23° 3·6;[7] tribenzyl, m. p. 92°,[8] 91·3°;[9] aniline, b. p. 184·5°/750 mm., d_4^{20} 1·0221, n_D^{20} 1·58547,[1] ε at 18° 7·316,[10] at 25° 6·90,[11] at 20° 7·21;[12] diphenyl, m. p. 53°;[13] triphenyl, m. p. 127°.[14]

Anilines: methyl, b. p. 193°/738 mm., d_4^{20} 0·9867,[1] 0·9863,[4] n_D^{20} 1·57094,[1] ε at 20° 5·8,[3] at 20·8° 5·93,[15] at 23° 5·3;[7] dimethyl, b. p. 194°/760 mm., d_4^{20} 0·9571, n_D^{20} 1·55776,[1] ε at 20° 5·07,[3] at 18° 5·0;[7] ethyl, b. p. 202·5°/750 mm., d_4^{20} 0·9601, n_D^{20} 1·55397,[1] ε at 19·8° 5·9,[15] at 20° 5·76,[16] at 19° 5·4;[6] diethyl, b. p. 214·5°/748 mm., d_4^{20} 0·9353,[1] 0·9344,[17] n_D^{20} 1·54178,[1] ε at 18·5° 5·5;[6] *n*-propyl, b. p. 96°/9 mm., d_4^{20} 0·9426, n_D^{20} 1·54217.[1]

[1] Vogel, *J.*, 1948, 1829—1833. [2] Turner and Merry, *J.*, 1910, **97**, 2069. [3] Schlundt, *J. Phys. Chem.*, 1901, **5**, 157. [4] Brühl, *Z. physikal. Chem.*, 1895, **16**, 193. [5] Walden, *ibid.*, 1910, **70**, 569. [6] Dobroserdov, *J. Russ. Phys. Chem. Soc.*, 1911, **43**, 124. [7] Mathews, *J. Phys. Chem.*, 1905, **9**, 665. [8] Mailhe, *Ann. Chim.*, 1920, **13**, 189. [9] Cannizzaro, *Jahresber.*, 1856, **9**, 582. [10] Turner, *Z. physikal. Chem.*, 1900, **35**, 385. [11] Lunt and Rau, *Proc. Roy. Soc.*, 1930, *A*, **126**, 213. [12] I.C.T., 1929, **6**, 82. [13] Leonard and Sutton, *J. Amer. Chem. Soc.*, 1948, **70**, 1565. [14] Piccard and Kharasch, *ibid.*, 1918, **40**, 1077. [15] Walden, *Z. physikal. Chem.*, 1910, **70**, 569. [16] Walden, Ulich, and Werner, *ibid.*, 1925, **116**, 261. [17] Richards and Mathews, *J. Amer. Chem. Soc.*, 1908, **30**, 10.

The values for the atomic refraction of nitrogen, calculated from the molecular refractions given in Table 10, are in most cases very close to Vogel's results (*loc. cit.*, p. 1825).

Solvents.—Hexane, *cyclo*hexane, carbon tetrachloride, benzene, and carbon disulphide were purified as previously described (Cowley and Partington, *J.*, 1933, 1252; 1936, 1184). The physical constants of the samples used are given with the individual measurements. Toluene was boiled under reflux with mercuric acetate solution, the yellow precipitate and water were removed, and the liquid washed with water and dried ($CaCl_2$ and finally Na); it was purified by

TABLE 11. *Properties of solutions of amines.*

10^6x_2	ε	d_4^{20}	P_{12}	P_2	10^6x_2	ε	d_4^{20}	P_{12}	P_2
				n-*Propylamine.*					
	In hexane.					In benzene.			
0	1·894	0·6695	29·55	—	0	2·283	0·8778	26·66	—
20,290	1·925	0·6695	30·14	58·6	19,638	2·327	0·8746	27·25	57·1
35,356	1·947	0·6696	30·53	57·3	35,374	2·362	0·8721	27·72	56·9
41,612	1·957	0·6697	30·71	57·5	49,012	2·393	0·8699	28·13	56·8
57,011	1·980	0·6699	31·11	56·9	59,127	2·416	0·8683	28·43	56·6
				Di-n-*propylamine.*					
	In hexane.					In benzene.			
0	1·894	0·6695	29·55	—	0	2·281	0·8779	26·62	—
14,255	1·907	0·6704	29·91	55·2	10,299	2·292	0·8757	26·93	56·7
20,840	1·913	0·6709	30·08	54·9	21,835	2·305	0·8732	27·29	57·1
26,384	1·918	0·6713	30·22	54·8	30,121	2·314	0·8714	27·54	57·1
32,963	1·924	0·6718	30·38	54·7	38,958	2·324	0·8695	27·82	57·3
				Tri-n-*propylamine.*					
				In benzene.					
0	2·283	0·8778	26·66	—	36,224	2·286	0·8679	27·82	58·9
12,565	2·285	0·8742	27·08	60·3	44,785	2·287	0·8657	28·10	58·9
30,463	2·286	0·8695	27·64	59·0					
				n-*Butylamine.*					
	In hexane.					In *cyclo*hexane.			
0	1·895	0·6693	29·58	—	0	2·019	0·7779	27·42	—
19,076	1·924	0·6702	30·19	61·4	14,813	2·045	0·7768	27·93	61·8
38,091	1·954	0·6710	30·80	61·6	29,968	2·072	0·7757	28·45	61·7
60,014	1·988	0·6720	31·48	61·2	35,868	2·083	0·7754	28·66	61·8
77,650	2·015	0·6727	32·00	60·7	48,802	2·107	0·7745	29·09	61·7
				In benzene.					
0	2·282	0·8779	26·64	—	24,838	2·342	0·8737	27·59	64·9
9,588	2·305	0·8763	27·00	64·1	30,436	2·355	0·8728	27·79	64·5
11,738	2·310	0·8760	27·08	64·4	49,102	2·401	0·8697	28·50	64·5
22,481	$2·336_5$	$0·8741_5$	27·50	64·8					

TABLE 11.—*Continued.*

10^6x_2	ε	d_4^{20}	P_{12}	P_2	10^6x_2	ε	d_4^{20}	P_{12}	P_2
				Di-n-butylamine.					
	In hexane.					In benzene.			
0	1·897	0·6763	29·33	—	0	2·276	0·8778	26·55	—
10,537	1·908	0·6775	29·71	65·7	10,894	2·288	0·8752	27·00	67·1
20,292	1·918	0·6785	30·06	65·4	22,805	2·300	0·8722	27·48	67·4
31,292	1·929	0·6797	30·45	65·1	31,014	2·310	0·8706	27·82	67·5
42,594	1·941	0·6809	30·86	65·3	38,517	2·318	0·8688	28·13	67·4
				cyclo*Hexylamine.*					
	In hexane.					In benzene.			
0	1·891	0·6695	29·47	—	0	2·280	0·8770	26·63	—
14,355	1·915	0·6720	30·03	68·6	12,101	2·306	0·8767	27·11	65·6
25,869	1·934	0·6740	30·48	68·4	23,661	2·332	0·8765	27·57	66·4
38,794	1·956	0·6762	30·97	68·2	36,209	2·360	0·8763	28·07	66·4
49,886	1·975	0·6782	31·40	68·1	46,486	2·380	0·8761	28·44	65·5
				Benzylamine.					
	In hexane.					In *cyclo*hexane.			
0	1·895	0·6693	29·58	—	0	2·019	0·7779	27·42	—
11,944	1·916	0·6727	30·05	68·9	14,160	2·047	0·7802	28·01	69·0
21,155	1·932	0·6752	30·41	68·6	21,370	2·062	0·7813	28·32	69·4
32,982	1·953	0·6783	30·87	68·7	30,090	2·078	0·7827	28·66	68·6
44,598	1·974	0·6814	31·33	68·8	40,399	2·099	0·7843	29·10	68·9
	In benzene.					In toluene.			
0	2·280	0·8789	26·58	—	0	2·379	0·8643	33·57	—
11,969	2·312	0·8804	27·11	71·3	13,516	2·405	0·8657	34·02	66·4
22,499	2·340	0·8818	27·58	71·0	24,369	2·427	0·8671	34·38	66·8
31,638	2·364	0·8828	27·98	70·9	33,706	2·447	0·8683	34·72	67·5
42,394	2·394	0·8843	28·47	71·1	44,356	2·467	0·8695	35·05	66·9
				Dibenzylamine.					
	In hexane.					In benzene.			
0	1·898	0·6698	29·64	—	0	2·280	0·8775	26·62	—
14,489	1·923	0·6778	30·47	87·1	12,621	2·306	0·8815	27·39	87·3
25,612	1·942	0·6840	31·10	86·7	24,398	2·331	0·8853	28·12	88·2
39,251	1·967	0·6919	31·89	87·1	35,737	2·354	0·8888	28·82	88·1
49,468	1·984	0·6973	32·47	86·9	44,028	2·371	0·8914	29·33	88·1
				Tribenzylamine.					
				In benzene.					
0	2·280	0·8779	26·61	—	24,583	2·321	0·8903	28·59	107·1
8,356	2·294	0·8823	27·28	106·7	31,811	2·333	0·8937	29·18	107·4
16,687	2·308	0·8864	27·94	106·7					
10^6x_2	n_D^{20}	d_4^{20}	$[R_D]_{12}$	$[R_D]_2$	10^6x_2	n_D^{20}	d_4^{20}	$[R_D]_{12}$	$[R_D]_2$
0	1·5009	0·8779	26·21	—	25,922	1·5082	0·8911	$27·94_5$	93·25
8,900	1·5035	0·8824	26·81	93·51	33,361	1·5103	0·8948	$28·45_5$	93·59
16,127	1·5055	0·8861	27·29	93·24	38,773	1·5117	0·8974	28·82	93·49
20,193	1·5066	0·8882	27·56	93·27				$[R_D]_{\infty}$	93·4
10^6x_2	ε	d_4^{20}	P_{12}	P_2	10^6x_2	ε	d_4	P_{12}	P_2
				Aniline.					
	In carbon tetrachloride.					In carbon disulphide.			
0	2·236	1·5941	28·15	—	0	2·641	1·2639	21·30	—
10,375	2·268	1·5887	28·65	75·8	10,953	2·695	1·2593	21·88	74·5
20,312	2·300	1·5835	29·13	76·2	21,846	2·749	1·2548	22·46	74·3
30,837	2·334	1·5778	29·64	76·3	32,312	2·799	1·2506	22·99	73·6
41,194	2·368	1·5724	30·14	76·4	42,975	2·852	1·2463	23·54	73·5
					In tetralin.				
0	2·757	0·9682	50·43	—	35,990	2·834	0·9693	51·18	71·2
11,513	2·782	0·9686	50·68	72·1	45,918	2·857	0·9696	51·42	71·9
23,054	2·806	0·9689	50·92	71·5					
				Diphenylamine.					
	In hexane.					In benzene.			
0	1·894	0·6695	29·55	—	0	2·280	0·8779	26·61	—
13,028	1·917	0·6763	30·20	79·8	11,632	2·307	0·8824	27·22	79·2
19,451	1·928	0·6796	30·52	79·3	22,214	2·332	0·8864	27·80	80·1
24,608	1·938	0·6825	30·79	79·9	34,819	2·361	0·8912	28·46	80·0
31,324	1·950	0·6860	31·12	79·8	43·696	2·383	0·8945	28·96	80·4

TABLE 11.—*Continued.*

10^6x_2	n_D^{20}	d_4^{20}	$[R_D]_{12}$	$[R_D]_2$	10^6x_2	n_D^{20}	d_4^{20}	$[R_D]_{12}$	$[R_D]_2$
				In benzene.					
0	1·5002	0·8779	26·18	—	34,374	1·5106	0·8913	27·29	58·44
17,504	1·5055	0·8845	26·74	58·34	39,174	1·5118	0·8930	27·44	58·29
24,203	1·5074	0·8872	26·95	57·99	45,791	1·5136	0·8955	27·64	58·08
31,059	1·5095	0·8900	27·17	57·99				$[R_D]_\infty$	58·2

10^6x_2	ε	d_4^{20}	P_{12}	P_2	10^6x_2	ε	d_4^{20}	P_{12}	P_2
				Triphenylamine.					
				In benzene.					
0	2·283	0·8779	26·65	—	28,625	2·333	0·8940	28·53	92·1
10,653	2·302	0·8839	27·35	92·4	29,785	2·335	0·8947	28·60	92·0
21,656	2·320	0·8901	28·05	91·4					

10^6x_2	n_D^{20}	d_4^{20}	$[R_D]_{12}$	$[R_D]_2$	10^6x_2	n_D^{20}	d_4^{20}	$[R_D]_{12}$	$[R_D]_2$
0	1·5009	0·8779	26·21	—	27,936	1·5124	0·8938	27·81	83·65
10,200	1·5052	0·8838	26·79	83·15	35,696	1·5155	0·8977	28·26	83·80
15,173	1·5072	0·8867	27·07	82·89	41,657	1·5180	0·9016	28·51	83·20
20,744	1·5095	0·8897	27·39	83·24				$[R]_{D\infty}$	83·3

10^6x_2	ε	d_4^2	P_{12}	P_2	10^6x_2	ε	d_4^{20}	P_{12}	P_2
				Methylaniline.					
		In hexane.					In benzene.		
0	1·884	0·6694	29·30	—	0	2·285	0·8771	26·71	—
11,256	1·916	0·6726	30·05	96·1	10,918	2·331	0·8786	27·43	92·8
23,588	1·951	0·6760	30·86	95·4	20,947	2·373	0·8799	28·09	92·5
34,817	1·983	0·6791	31·58	94·8	30,680	2·414	0·8815	28·71	91·8
45,327	2·013	0·6820	32·24	94·3	41,766	2·461	0·8830	29·42	91·6
				Dimethylaniline.					
		In hexane.					In benzene.		
0	1·884	0·6694	29·30	—	0	2·280	0·8788	26·58	—
10,764	1·911	0·6725	29·98	92·5	10,457	2·320	0·8800	27·28	93·1
18,889	1·932	0·6749	30·50	92·7	21,653	2·362	0·8812	28·01	92·5
29,121	1·958	0·6779	31·13	92·2	30,329	2·395	0·8822	28·57	92·3
38,109	1·982	0·6807	31·70	92·4	40,418	2·432	0·8832	29·21	91·7
				Ethylaniline.					
				In hexane.					
0	1·884	0·6694	29·30	—	31,829	1·975	0·6787	31·54	99·8
11,151	1·915	0·6727	30·09	100·1	41,780	2·004	0·6814	32·24	99·8
20,752	1·943	0·6755	30·76	99·9					
				Diethylaniline.					
		In hexane.					In benzene.		
0	1·895	0·6713	29·49	—	0	2·276	0·8787	26·53	—
11,215	1·932	0·6751	30·51	119·7	10,248	2·327	0·8796	27·48	119·9
20,519	1·964	0·6784	31·35	120·1	20,933	2·380	0·8807	28·48	119·7
29,604	1·994	0·6814	32·16	119·4	30,117	2·426	0·8815	29·33	119·5
41,635	2·033	0·6855	33·18	118·0	39,342	2·472	0·8824	30·18	119·4
				n-*Propylaniline.*					
		In hexane.					In benzene.		
0	1·885	0·6694	29·32	—	0	2·285	0·8776	26·69	—
10,132	1·914	0·6727	30·09	104·7	11,285	2·333	0·8790	27·56	103·9
19,195	1·940	0·6756	30·76	104·4	22,132	2·379	0·8805	28·39	103·5
29,943	1·972	0·6790	31·58	104·9	26,563	2·399	0·8808	28·75	104·3
40,568	2·004	0·6822	32·40	105·1	34,561	2·432	0·8818	29·34	103·4
					43,419	2·470	0·8831	30·01	103·1
				Ethyl-n-*propylaniline.*					
		In hexane.					In benzene.		
0	1·895	0·6713	29·49	—	0	2·284	0·8779	26·67	—
11,190	1·932	0·6755	30·54	123·0	14,572	2·356	0·8791	28·10	124·7
22,552	1·971	0·6799	31·61	123·5	24,313	2·404	0·8799	29·05	124·5
33,566	2·006	0·6835	32·60	122·1	29,969	2·432	0·8804	29·60	124·5
43,256	2·039	0·6870	33·51	122·3	40,622	2·483	0·8814	30·61	123·8

several fractionations. Tetralin was purified by drying ($CaCl_2$) and repeated fractionation under reduced pressure : b. p. 69·5—71·5°/1 mm., d_4^{20} 0·9682, ε at 20° 2·757. Govinda Rau and Satyanarayana Rao (*Proc. Indian Acad. Sci.*, 1935, *A*, **2**, 232) give d_4^{20} 0·9679, ε at 20° 2·756.

Results.—The molar polarisations of the solvent, solution, and solute are expressed by P_1, P_{12}, and P_2, respectively. The mole-fraction x_2 of the solute and the dielectric constant and density of the solution are given and all results refer to 20·0°. The extrapolated value of the polarisation of the solute at infinite dilution, $P_{2\infty}$, is given in Table 1 with the dipole moment. In the majority of the measurements recorded in Table 11, the change of P_2 with concentration is small and the uncertainty in the extrapolation should not be greater than a few tenths of a c.c.

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681. *Studies in Co-ordination Chemistry. Part XIII.* Magnetic Moments and Bond Types of Transition-metal Complexes.*

By F. H. Burstall and R. S. Nyholm.

The magnetic moments of octahedral complexes of chromium, manganese, iron, cobalt, and nickel with the chelate groups dipyridyl and a ditertiary arsine are compared. Many of these moments are reported for the first time and the following new compounds are described : $[Co(Diarsine)_3](ClO_4)_2$, $[Co(Diarsine)_3](ClO_4)_3$, $[Co(Diarsine)_2(OAc)_2](ClO_4)$, $[Co(Dipy)_3](ClO_4)_3 3H_2O$, and $[Cr(Dipy)_2Cl_2]Cl,2H_2O$, where Diarsine = *o*-phenylenebisdimethylarsine and Dipy = 2 : 2′-dipyridyl. Also, the co-ordination of tervalent chromium with a tertiary arsine is reported for the first time. The meaning of the terms " ionic " and " covalent " binding as deduced from magnetic data is discussed. In compounds of the type $[M^{II}(Dipy)_3]X_2$, the bonds are ionic ($4s4p^34d^2$) when M^{II} = Mn or Co and covalent ($3d^24s4p^3$) when the metal is Fe or Cr. The nature of the bonds in the corresponding nickel compounds is discussed and it is concluded that the paramagnetism indicates ionic rather than covalent bonds. In the dipyridyl complexes of tervalent Fe and Co the bonds are covalent but the magnetic data are not diagnostic when M^{III} = Cr. No ditertiary arsine complexes of bivalent Cr or Mn were isolated but Fe, Co, and Ni, in their bi- and ter-valent states, all form stable octahedral complexes with this chelate group ; in every case the moments indicate $3d^24s4p^3$ covalent bonds. Certain hypotheses to account for the observed data are proposed. In all cases the moments are consistent with Pauling's theory relating bond type and stereochemistry with magnetic moments.

In a recent series of investigations (Nyholm, *J.*, 1950, 851, 2061, 2071 ; 1951, 38, 2602) the complexes formed by iron, cobalt, nickel, and copper with the ditertiary arsine chelate group, *o*-phenylenebisdimethylarsine, $C_6H_4(AsMe_2)_2$, were described and their magnetic moments reported. The bivalent complexes of iron, cobalt, and nickel with this chelate group may be oxidised, even by air, to the tervalent compounds which contain strong covalent bonds. The tervalent nickel complexes contain one unpaired electron but these compounds, and particularly the diamagnetic complex salt $[Ni(Diarsine)_3](ClO_4)_2$, earlier led to some difficulties of interpretation on the simple Pauling theory relating magnetic moment, bond type, and stereochemistry. Also, in contrast with the stability of the iron, cobalt, and nickel compounds, chromium and manganese were reluctant to co-ordinate with the ditertiary arsine. It was considered that a comparative study of the magnetic behaviour of all five metals with dipyridyl and the ditertiary arsine might throw some light on these problems and, accordingly, a summary of the data available in the literature was made. Surprisingly, although dipyridyl complexes of all of these metals have been known for some time, the magnetic moments of several of them had not been reported. These

* Part XII, *J.*, 1952, 2906.

outstanding values have been determined and the results of this and of previous investigations are summarised in Table 1 and 2. In several cases the values reported by previous workers have been checked.

TABLE 1. *Magnetic susceptibilities of various octahedral complexes.*

Compound	$\chi_g \times 10^{-6}$	$\chi_M \times 10^{-6}$	Diamag. corr.	$\chi_M \times 10^{-6}$, corr.	μ (B.M.)	Ref.
Bivalent : dipyridyl						
$[Cr(Dipy)_3][Br]_2,4H_2O$	5·57	4,190	375	4,565	3·27	7
$[Mn(Dipy)_3][Br]_2$	21·6	14,800	355	15,155	5·98	
$[Fe(Dipy)_3][ClO_4]_2$	−0·27	−225	—	—	0·0	1, 7
$[Co(Dipy)_3][ClO_4]_2$	13·2	9,660	350	10,010	4·85	7; cf. 2
$[Ni(Dipy)_3][I]_2,6H_2O$	4·16	3,700	449	4,149	3·10	7; ,, 2
$[Ni(Dipy)_3][ClO_4]_2$	5·23	3,800	350	4,150	3·10	7;
Bivalent : diarsine						
$[Fe(Diarsine)_3Br_2]^0$	−0·3	−236	—	—	0·0	3
$[Co(Diarsine)_3][ClO_4]_2$	0·85	945	648	1,593	1·92	7
$[Ni(Diarsine)_3][ClO_4]_2$	−0·38	−423	—	—	0·0	4
Tervalent : dipyridyl						
$[Cr(Dipy)_3][ClO_4]_3$	6·77	5,610	374	5,984	3·76	7
$[Cr(Dipy)_2Cl_2]Cl,2H_2O$	12·80	6,480	260	6,740	3·98	,,
$[Fe(Dipy)_3][ClO_4]_3,3H_2O$ ...	2·32	2,030	405	2,435	2·36	5, 7
$[Co(Dipy)_3][ClO_4]_3,3H_2O$ ...	−0·35	−308	—	—	0·0	7
Tervalent : diarsine						
$[Fe(Diarsine)_2Cl_2]ClO_4$	2·33	1,860	461	2,320	2·34	3
$[Co(Diarsine)_3][ClO_4]_3$	−0·39	−474	—	—	0·0	7
$[Co(Diarsine)_2Cl_2]ClO_4$	−0·50	−400	—	—	0·0	6
$[Ni(Diarsine)_2Cl_2]Cl$	1·42	1,055	452	1,507	1·89	4

References : (1) Berkmann and Zocher, *Z. physikal. Chem.*, 1926, **124**, 318; Sidgwick, " Electronic Theory of Valency," Oxford, 1927, p. 163; cf. Klemm, Jacobi, and Tilk, *Z. anorg. Chem.*, 1931, **201**. 1. (2) Asmussen, " Magnetokemiske Undersgelser Over Uorganiske Kompleksforbindelser," Copenhagen, 1944, p. 212; Cambi and Cagnasso, *Atti R. Accad. Lincei Rend.*, 1934, **19**, 458; cf. Cambi, Cagnasso, and Tremolada, *Gazzetta*, 1934, **64**, 758. (3) Nyholm, *J.*, 1950, 851. (4) *Idem*, *ibid.*, p. 2061. (5) Simon, Morgenstern, and Albrecht, *Z. anorg. Chem.*, 1937, **230**, 225; A. Simon and Knauer, *Z. Electrochem.*, 1939, **45**, 678; cf. Walden, Hammett, and Gaines, *J. Chem. Phys.*, 1935, **3**, 364; *J. Amer. Chem. Soc.*, 1936, **58**, 1668; see also Michaelis and Granick, *ibid.*, 1943, **65**, 481. (6) Nyholm, *J.*, 1950, 2071. (7) This work.

Table 2. *Experimental and calculated magnetic moments of octahedral transition-metal complexes.*

	Cr	Mn	Fe	Co	Ni	Cr	Mn	Fe	Co	Ni
	Bivalent compounds					Tervalent compounds				
Calculated magnetic moment for ionic or $4s4p^34d^2$ bonds	4·90	5·92	4·90	3·88	2·83	3·88	4·90	5·92	4·90	3·88
Calculated magnetic moment for covalent $3d^24s4p^3$	2·82	1·73	0·00	1·73	0·00 *	3·88	2·83	1·73	0·00	1·73
Experimental moment of dipyridyl complex	3·27	5·98	0·00	4·85	3·10	3·76	†	2·35	0·00	†
Experimental moment of diarsine complex	†	†	0·00	1·92	0·00	3·9	†	2·35	0·00	1·9

* It is assumed that two electrons are promoted from a 3*d* to a 5*s* orbital in which they are paired.
† Not isolated.

Before discussing these data, it is desirable to comment upon the use of magnetic measurements for distinguishing between " covalent " and so-called " ionic " bonds in metal complexes. These two terms are commonly used to distinguish between two extreme types of binding but the limitations of this terminology are fully recognised. By " covalent " binding is implied the use of strong covalent bonds using deep seated orbitals of the metal atom with maximum electron pairing; by " ionic " binding is meant the formation of bonds without any electron pairing at all, *i.e.*, the moment is the same as that of the free ion when Hund's rule of maximum multiplicity of spins is obeyed. In, *e.g.*, the octahedral complexes of tervalent iron, it is found in practice that the moments are either about 2·3 or 5·9 Bohr magnetons, indicating one and five unpaired electrons respectively if the orbital contribution be ignored in the first case. Those complexes containing one unpaired electron are considered to use octahedral $3d^24s4p^3$ bond orbitals, the two 3*d*

orbitals being made available for bond formation by electron pairing; potassium ferricyanide is an example of this class of compound. In the more strongly paramagnetic complexes containing five unpaired electrons, *e.g.*, potassium ferrioxalate, none of the five 3*d* orbitals is available for bond formation and hence the moment is the same as if the bonds between the Fe(III) ion and the three oxalate groups were purely electrostatic. However, an Fe(III) complex with five unpaired electrons might also make use of $4s4p^34d^2$ orbitals in resonance with these ionic bonds. The physical properties of ferric trisacetylacetone, for example, are such that this compound certainly has some type of covalent bonds present; it dissolves in various organic solvents and volatilises when heated. The magnetic moment precludes the use of $3d^24s4p^3$ bond orbitals and it is considered that higher (4*d*) orbitals are brought into play. This proposal has also been made by Professor Jensen (see Report of the Co-ordination Chemistry Conference, *Nature*, **1951**, **167**, 434). Huggins (*J. Chem. Phys.*, **1937**, **5**, 527) had earlier suggested that $4s4p^34d^2$ bond orbitals might be used in certain transition-metal complexes.

Pauling (*J.*, **1948**, 1461) pointed out that the term " ionic " must not be taken too literally and discussed the possibility of using higher-level covalent-bond orbitals; the possibility of four $4s4p^3$ covalent bond orbitals resonating among the six positions was suggested. Many other workers, *e.g.*, Sugden (*J.*, **1943**, 328), have commented upon the unfortunate connotations of the term " ionic." A recent theoretical investigation (Craig, Maccoll, Nyholm, Orgel, and Sutton, unpublished; see also Orgel, *Nature*, **1951**, **167**, 434) has shown that the use of the higher 4*d* orbitals for σ bond formation by the transition metals is quite feasible from overlap calculations; further, it has been found that the atoms which favour the use of the 4*d* orbitals of a transition metal are the more electronegative ones, as found in practice for so-called " ionic " bonds. The use of $4s4p^34d^2$ octahedral bond orbitals should result in bonds which are weaker than those derived from the use of the more deep-seated $3d^24s4p^3$ orbitals. The fact that the use of higher covalent bond orbitals in the so-called " ionic " complexes is quite feasible and permits of a more satisfactory description of a bond whose properties are essentially covalent in the usual sense, raises the point whether one could refer to complexes as using " higher " and " lower " covalent bond orbitals rather than as possessing " ionic " and " covalent " bonds respectively. The terms " Normalkomplexe " and " Durchdringungskomplexe " are already commonly used to describe these types. This subject will be discussed further by Craig *et al.*

In Tables 1 and 2 the predicted magnetic moments have been calculated on the spin-only formula, $\mu = \sqrt{n(n+2)}$ Bohr magnetons, where n is the number of unpaired electrons per metal atom. For the transition metals it is commonly assumed that the orbital contribution is negligibly small, but it can be quite appreciable in some cases, *e.g.*, bivalent cobalt. The size of this orbital contribution, however, is never such as to lead to any ambiguity as to the number of unpaired electrons in the complexes under examination. Given the number of spins, and the co-ordination number of the metal, the orbitals used for bond formation may often be inferred if a suitable theory is accepted. In Pauling's theory the bond orbitals required for a given shape, here d^2ps^3, are made available either by pairing electrons at lower (3*d*) levels or by elevating them to orbitals above those used for bond formation : an example of the former process is the formation of the diamagnetic ferrous compounds starting with a ferrous ion containing four unpaired electrons; the second type of process is postulated to explain the moment of the $[Co(NO_2)_6]^{4-}$ ion which contains only one unpaired electron instead of the three in the cobaltous ion. This unpaired electron is believed to be promoted to an orbital above the $3d^24s4p^3$ orbitals used for bond formation (Pauling, *loc. cit.*, p. 97). Where this promotion occurs it is to be expected that this electron should be in an excited state and capable of being removed by oxidation fairly easily. With the $[Co(NO_2)_6]^{4-}$ ion this is so, but it is probable that this process of promotion is less common than is often supposed; this is referred to later (p. 3574). An alternative approach to the problem of magnetic moment and complex formation has been made by Van Vleck (" The Theory of Magnetic and Electric Susceptibilities," **1935**, Oxford, p. 282; *J. Chem. Phys.*, **1935**, **3**, 807). According to his argument the atom retains its spin multiplicity if the co-ordinated groups are not held to the metal atom by strong forces and hence the magnetic moment of the complex ion is the same as that of the free ion; this is assumed

to occur in the $[FeF_6]^{3-}$ ion in which the forces are assumed to be ionic as in the hydrates. With the $[Fe(CN)_6]^{3-}$ ion, on the other hand, the formation of strong covalent bonds is considered to upset the Russell–Saunders coupling, giving rise to a complex ion containing the smallest rather than the greatest number of unpaired spins, as would be expected from Hund's rule of maximum multiplicity. Fortunately, both theories lead to the same result so far as the moment is concerned in the complexes under examination. Most of the literature has been interpreted in terms of Pauling's theory and that approach is adopted here. Reduction of the moment by Van Vleck's mechanism possibly occurs in certain fluorides of the transition metals, *e.g.*, CoF_3; these are reported upon in more detail by Nyholm and Sharpe (Part XII, *J.*, 1952, 2906).

All magnetic susceptibilities were measured at room temperatures and corrected to 20°, Curie's law ($\chi_M \propto 1/T$) being assumed. In view of the magnetic dilution and small temperature difference from 20° this seems quite justifiable.

In calculating moments in Table 1, allowance has been made for atomic diamagnetism of atoms other than the metal atom itself. As mentioned on p. 3572, moments which are 0·2—0·4 B.M. in excess of the calculated figure for spin only do not lead to any ambiguity, but the apparent moments of certain diamagnetic compounds call for comment. Compounds such as $[Fe(Dipy)_3][ClO_4]_2$ have moments of as much as 0·6—0·7 B.M. after the necessary diamagnetic correction to the molar susceptibility has been made. However, since the magnetic moment is proportional to the square root of the corrected molar susceptibility, $\mu = 2{\cdot}84\sqrt{\chi_{corr.} \times T}$, it can be shown that a moment of 0·6 B.M. arises from a corrected molar susceptibility of only one-tenth of that required for one unpaired electron. Here we have listed all moments which are less than 0·7 B.M. as formally 0·0, since it is practically certain that they arise from factors other than electron spin. The following could account for these small moments: (*a*) experimental errors in the determination; (*b*) impurity of the compound; (*c*) uncertainty in the diamagnetic correction for atomic diamagnetism; (*d*) temperature-independent paramagnetism. The effect probably arises from a combination of all of these but the correction for diamagnetism in particular is very uncertain in many cases.

Discussion of Results.—The preparation of the various compounds is described in the Experimental section. Wherever possible an attempt was made to obtain the compound in which three molecules of the chelate group are attached to the metal atom, but in some cases compounds in which only two molecules of the chelate are attached were isolated. This occurs most frequently with the tervalent metals and may be caused by the tendency to reduce the charge on the complex ion.

Chromium.—Trisdipyridylchromous bromide was described by Barbieri and Tettamanzi (*Atti R. Accad. Lincei*, 1932, **15**, 877) as the black hexahydrate; using a similar method of preparation, we obtained a tetrahydrate on drying. The moment of this compound (3·27 B.M.) indicates $3d^24s4p^3$ bonds. The complex cyanide $K_4Cr(CN)_6$, for which Hume and Stone (*J. Amer. Chem. Soc.*, 1943, **65**, 1200) reported $\mu = 3{\cdot}15$ B.M., seems to be the only other bivalent chromium complex known in which electron pairing occurs. These authors also report the moments of a large number of chromous complexes containing ionic bonds. With tervalent chromium the compounds $[Cr(Dipy)_3][ClO_4]_3$, first prepared by Barbieri and Tettamanzi (*loc. cit.*), and $[Cr(Dipy)_2Cl_2]Cl,2H_2O$ were isolated, but the magnetic moments (*ca.* 3·9 B.M.) give no information as to the bond type since both ionic and $3d^24s4p^3$ bonds result in the presence of three unpaired electrons. No chromous complexes of the ditertiary arsine were isolated but tervalent chromium forms a readily hydrolysable deep blue complex of the probable formula $[CrCl_2(Diarsine)(H_2O)(C_2H_5{\cdot}OH)]Cl$; however, the moment is again *ca.* 3·9 B.M. and is not diagnostic of bond type but is recorded to show that no electron pairing occurs.

Manganese.—The moment of the compound $[Mn(Dipy)_3]Br_2$ indicates five unpaired electrons, showing that no electron pairing occurs. Goldenberg (*Trans. Faraday Soc.*, 1940, **36**, 847) has summarised the magnetic data for a large number of manganese compounds and finds that for Mn(II) electron pairing occurs in the complex cyanide $K_4[Mn(CN)_6],3H_2O$ only; the moment of this compound is 2·18 B.M. All attempts to obtain complex compounds of manganese with the ditertiary arsine have failed.

Iron.—The red trisdipyridylferrous complexes have been reported by several workers to be diamagnetic, with $3d^2 4s 4p^3$ bonds. The related chelate group *p*-phenanthroline behaves similarly. Tervalent iron forms both a blue trisdipyridyl ion, $[Fe(Dipy)_3]^{3+}$, and a brown binuclear ion $[(Fe(Dipy)_2(OH)_2]^{4+}$, for both of which the magnetic moments (2·1—2·4 B.M.) indicate $3d^2 4s 4p^3$ bonds (see references to Table 1). No compounds of the type $[Fe(Diarsine)_3]X_2$ have been isolated, but those with the formula $[Fe(Diarsine)_2X_2]^0$ are diamagnetic; ferric iron forms the cation $[Fe(Diarsine)_2X_2]^+$ (X = Cl or Br) very readily, and in both ferrous and ferric compounds the moments indicate $3d^2 4s 4p^3$ bonds (see Part III, *J.*, 1950, 851).

Cobalt.—Cobaltous compounds of the type $[Co(Dipy)_3]X_2$ were first described by Blau (*Monatsh.*, 1896, **19**, 647) but the magnetic moment has not been measured previously. The moment of the perchlorate (4·85 B.M.) indicates ionic bonds. For the bromide of the corresponding *o*-phenanthroline complex, Cambi and Cagnasso (*Atti R. Accad. Lincei*, 1934, **19**, 458) reported the value 5·1 B.M. The tervalent cobalt compound $[Co(Dipy)_3][ClO_4]_3,3H_2O$, like all octahedral cobalt complexes with the exception of the fluoride, is diamagnetic with $3d^2 4s 4p^3$ bonds. By variation of the technique used in Part V (*J.*, 1950, 2071), the trisdiarsine complex $[Co(Diarsine)_3][ClO_4]_2$ has been isolated, one molecule of the chelate being replaced fairly readily in the presence of suitable substituents. The magnetic moment of this compound (1·92 B.M.) indicates maximum electron pairing and $3d^2 4s 4p^3$ bonds. As mentioned previously, it is necessary to promote this unpaired electron into a higher orbital in order to make the $3d^2 4s 4p^3$ octahedral bond orbital available for bond formation. This electron probably goes into a 5*s* orbital where its removal by oxidation should take place easily. This is in accord with our observation that in aqueous-alcoholic solution the compound $[Co(Diarsine)_3][OAc]_2$ is oxidised rapidly by air to the corresponding cobaltic compound which was isolated as the diamagnetic perchlorate. In the presence of acetic acid in excess, this cobaltic complex loses one molecule of the chelate group to give a red, diamagnetic bisacetato-compound with the formula $(Co(Diarsine)_2(OAc)_2]ClO_4$. The trisdiarsine compound offers a unique opportunity for the resolution of an octahedral cobaltous compound with covalent bonds; preliminary indications that this can be achieved have already been obtained by Dr. D. D. Brown, with whom the resolution of this substance and its oxidation product is being investigated.

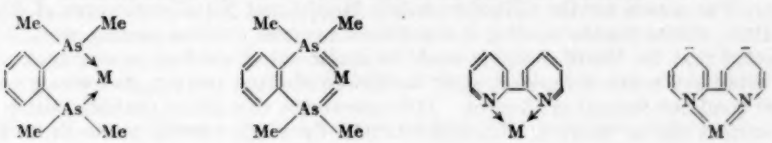
Nickel.—The red trisdipyridyl complexes of bivalent nickel have been studied by many workers since they were first prepared by Blau (*loc. cit.*). The resolution of the $[Ni(Dipy)_3]^{++}$ ion by use of active tartaric acid (Morgan and Burstall, *J.*, 1931, 2213) proves that the six bonds are octahedral. The moment has been measured by many investigators (see Table 1), and although values varying between 2·8 and 3·1 B.M. have been reported, the disagreement is unimportant here since the results unambiguously indicate the presence of two unpaired electrons. However, the orbitals which these two orbital electrons occupy have been the subject of much discussion (see Pauling, *loc. cit.*, p. 117; Palmer, "Valency Theory," Cambridge, 1944, p. 178; Emeléus and Anderson, "Modern Aspects of Inorganic Chemistry," Routledge, 1938, p. 176). We take the view that no promotion of electrons occurs in this ion, the two unpaired electrons still being in a 3*d* shell. If this promotion did occur, allowing $3d^2 4s 4p^3$ bonds to be used, then the two unpaired electrons would be promoted either to a 5*s* orbital in which their spins would be paired, or, less likely, remain unpaired by being promoted one to a 5*s* and one to a 5*p* orbital. In the accepted sequence of energy levels, the 5*s* is below the 4*d* and, following the usual procedure in atom building, it is always found that two *paired* electrons are placed in an *s* orbital before the filling up of *p* orbitals begins. Thus we expect that, if the bonds were $3d^2 4s 4p^3$, then the ion would be diamagnetic whereas the observed paramagnetism, corresponding with two unpaired electrons, suggests that two unpaired 3*d* electrons are present and hence that the bonds are ionic ($4s 4p^3 4d^2$). The fact that oxidation of the trisdipyridyl nickel complex to a compound of quadrivalent nickel has not been achieved supports this view. Furthermore, the proposal is consistent with the observed diamagnetism of the $[Ni(Diarsine)_3]^{++}$ ion, which is much more stable, suggesting the use of $3d^2 4s 4p^3$ bond orbitals. The use of 4*d* orbitals for σ bond formation is discussed in more detail by Craig *et al.* (*loc. cit.*) where further support for the above view is adduced. The

compound $[Ni(Diarsine)_3][ClO_4]_2$ was isolated as a deep red powder (Part V, *J.*, 1950, 2061) during the preparation of compounds of the type $[NiCl_2(Diarsine)_2]Cl$. The former is not oxidised by air, but in aqueous solution it is oxidised immediately by chlorine, ceric sulphate, or permanganate to give a green solution; addition of perchloric acid to the solution produces a yellowish-green perchlorate which apparently contains tervalent nickel since it is paramagnetic. Unfortunately, the compound could not be obtained pure because on oxidation there is a marked tendency to lose one molecule of tertiary arsine; nevertheless, the fact that $[Ni(Diarsine)_3][ClO_4]_2$, unlike the dipyridyl complex, can be oxidised supports the view that the bonds are $3d^2 4s 4p^3$. Many tervalent nickel complexes of the type $[NiX_2(Diarsine)_2]Y$ have been isolated, all having a magnetic moment corresponding with one unpaired electron. Still further oxidation of these compounds yields deep blue complexes of the type $[NiCl_2(Diarsine)_2][ClO_4]_2$, the diamagnetism of which indicates that the nickel atom is now quadrivalent (Part IX, *J.*, 1951, 2602). The isolation of these Ni(IV) complexes provides strong support for the electronic arrangement proposed for the Ni(II) and Ni(III) complexes.

Before attempting to account for the electron pairing it is desirable to summarise some general conclusions from a survey of the experimental results. (1) Whereas dipyridyl may co-ordinate with these transition metals by means of ionic *or* covalent bonds, the ditertiary arsine forms complexes containing covalent bonds only. (2) Manganese and, to a lesser extent, chromium show the greatest reluctance to co-ordinate with the ditertiary arsine; the reluctance of these metals to co-ordinate with the less electronegative ligands has been noted by Sidgwick ("The Chemical Elements and Their Compounds," Oxford, 1950, pp. 1010, 1286). (3) The magnetic moments of all of the compounds can be accounted for satisfactorily on Pauling's theory, by suitably pairing and promoting electrons where necessary; however, it is suggested that promotion occurs less readily than is sometimes assumed, the ligands making use of higher-level, but weaker, bonding orbitals. (4) Wherever both co-ordinate with the same metal the ditertiary arsine is more effective than dipyridyl in causing electron pairing. (5) As expected, both chelate groups co-ordinate more strongly than the corresponding simple, non-chelating ligands, pyridine and dimethylphenylarsine.

Much experimental evidence is available concerning the stability in aqueous solution of complex compounds of the first transition series with a variety of ligands (Burkin, *Quart. Reviews*, 1951, **5**, 1); most of the work concerns the metals in their bivalent states and is therefore relevant to this investigation. Examination of the work of Mellor and Maley (*Nature*, 1947, **159**, 370; 1948, **161**, 436) and of Irving and Williams (*ibid.*, 1948, **162**, 746) reveals that, irrespective of the ligand used (provided that no electron pairing occurs), the order of stability of complexes of the first transition series in aqueous solution is $Mn^{II} < Fe^{II} < Co^{II} < Ni^{II} < Cu^{II} > Zn^{II}$. Except where steric effects are operative, the same order is preserved with polydentate groups (Schwarzenbach, *Angew. Chem.*, 1950, **62**, 218). Departures from this order have been attributed by Irving (see Report of Co-ordination Chemistry Conference; Wilkins, *Nature*, 1951, **167**, 434) to steric factors or to a change in the bond orbitals used for bond formation.

It is suggested that the major factor responsible for electron pairing and strong binding in certain of these compounds is the formation of strong double bonds (π bonds) using 3*d* electron pairs of the transition metal, as originally proposed by Pauling (*loc. cit.*, p. 250; see also more detailed references in Part X, *loc. cit.*) for complex cyanides, carbonyls, and nitro-complexes. In the case of dipyridyl the 3*d* electron pairs of the metal would need to make use of a *p* orbital of the nitrogen atom, whilst a vacant *d* orbital would be used with the arsenic atom of the ditertiary arsine. The single- and double-bond structures contributing to the resonance hybrid in each of the two cases are shown below:



The extent of double bonding will obviously be influenced by the nature of the ligand, the overlap between the *d* orbital of the metal and the vacant *p* or *d* orbital of the nitrogen or arsenic atom, and the number of 3*d* electrons of the metal available for bond formation. As mentioned on p. 3572, the theoretical feasibility of double bonds in these complexes has been established from overlap integral calculations (Orgel, Report of Co-ordination Chemistry Conference, *loc. cit.*). As for the relative ability of the ditertiary arsine and dipyridyl to form double bonds, it is noteworthy that, whereas in the former the use of an already vacant *d* orbital is involved, in the latter a redistribution of charge is necessary, leaving the carbon atom *para* to the nitrogen with a considerable negative charge. This could occur only to a limited extent, and therefore we might expect to find that double bonding was less with dipyridyl than with the ditertiary arsine. This view is supported by the values of the force constants of the C–O bonds in $Ni(CO)_4$, $Ni(CO)_2$Diarsine, and $Ni(CO)_2$Dipy (Nyholm and Short, unpublished). These are approximately $15{\cdot}9 \times 10^5$, $15{\cdot}6 \times 10^5$, and $14{\cdot}6 \times 10^5$. If we ascribe the gradual weakening of the C–O bond to increasing double-bond character in the Ni–C bond, then the percentage double-bond character decreases in the order Ni–C in $Ni(CO)_4$ is just > Ni–As in $Ni(CO)_2$Diarsine >Ni–N in $Ni(CO)_2$Dipy. This is in accord with other experimental observations. So far as data are available, all groups which cause electron pairing with the bivalent transition metals, *e.g.*, CN, NO_2, CO, tertiary arsines, tertiary phosphines, the glyoximes, etc., permit of double-bond structures being written. This does not hold for certain of the tervalent transition metals, *e.g.*, Co(III), which more closely resemble the heavier Group VIII metals as the valency increases, with a tendency to form strong covalent bonds with even the most electronegative atoms; thus, even the hexahydrate $[Co(H_2O)_6]_2(SO_4)_3$ is diamagnetic (Asmussen, *loc. cit.*).

We suggest that electron pairing occurs provided the σ bond is reasonably strong and where the double bonding occurs to an extent sufficient to promote electrons where necessary. Considering first the dipyridyl complexes, double bonding is sufficient to cause electron pairing with Cr(II) and Fe(II) but not with Mn(II), Co(II), and Ni(II). The failure to observe electron pairing with Mn(II) seems to lie partly in the weakness of the σ bond, indicated both by the position of Mn(II) in the Mellor–Maley series and by its low electronegativity, and partly in the peculiar stability of the half-filled 3*d* shell. An arrangement of five unpaired electrons is known from atomic theory to be associated with special stability and hence an even greater reluctance than usual for electron pairing to take place (see Pauling, Victor Henri Memorial Volume, Liége, 1948, p. 8). Another factor is operative in the cases of Co(II) and Ni(II); here the necessary $3d^24s4p^3$ orbitals can be made available only by promotion of electrons above the 4*p* level. To effect this promotion evidently requires the use of groups with greater capacity for double-bond formation than that which occurs with dipyridyl. On the other hand, the ditertiary arsine causes electron pairing with all three metals, Fe(II), Co(II), and Ni(II). This is taken to indicate that the ditertiary arsine forms double bonds much more readily than dipyridyl, thus overcoming the expected weakness of the σ bond arising out of the lower donor capacity of arsenic as compared with nitrogen. Table 3 shows the relative capacities of different groups to effect electron pairing along the sequence iron, cobalt, and nickel. The cyanide group has not been included since this forms four-covalent rather than octahedral complexes with Ni(II). If they can be isolated it is expected that Cr(II) complexes of the diarsine will involve electron pairing and $3d^24s4p^3$ bonds.

With the tervalent elements, dipyridyl complexes of Cr(III), Fe(III), and Co(III) have been isolated and the magnetic moment agrees with $3d^24s4p^3$ binding in all cases; Cr(III) is uncertain, since the magnetic moment is not diagnostic of bond type, but the marked stability of Cr(III) complexes makes it very probable that lower *d* orbitals are used in the binding. The reason for the failure to isolate Mn(III) and Ni(III) complexes of dipyridyl is uncertain, unless double bonding is insufficient to cause electron pairing, since it would be expected that the Ni(III) complex would be stable only if electron pairing took place.

All ditertiary arsine complexes show maximum electron pairing, and strong covalent $3d^24s4p^3$ bonds are formed in all cases. It is noteworthy that either electron pairing occurs or no complex can be isolated; this suggests that the single σ bonds are weak, at least in

comparison with dipyridyl, and that double bonding is a major factor in their stability. This is not unlikely since it is known that there is some parallel between the proton affinity of a ligand and its ability to co-ordinate with metals which cannot form double bonds, *e.g.*, boron; whereas dipyridyl definitely has some basic tendencies, forming salts with strong acids, the ditertiary arsine will not do this. The reluctance of manganese to co-ordinate is again evident and is attributed to the reasons given above.

Several possibilities for further investigation arise out of this survey. It will be of interest to compare the ability of various substituted dipyridyl derivates to co-ordinate with transition metals on the one hand and with those which cannot form double bonds on the other. Thus, of 4 : 4′-dimethyl- and 4 : 4′-dichloro-2 : 2′-dipyridyl, the former should have the higher basicity and hence the greater co-ordinating ability towards metals which do not form double bonds. However, the chloro-derivative is the one which favours de-localisation of charge from the nitrogen and hence the formation of double bonds.

TABLE 3. *Effect of various groups on type of binding in metal complexes.*

Group and complex	Transition metal and type of binding		
	Fe^{II}	Co^{II}	Ni^{II}
Ethylenediamine $[M(en)_3]^{2+}$	Ionic [1]	Ionic [2]	Ionic [3]
Dipyridyl $[M(Dipy)_3]^{2+}$	Covalent [4]	Ionic [4]	Ionic [4]
Nitrite group $[M(NO_2)_6]$	Covalent [5]	Covalent [5]	Ionic [6]
Diarsine group $[M(Diarsine)_3]^{2+}$ or $[M(Diarsine)_2X_2]^0$	Covalent [4]	Covalent [4]	Covalent [4]

References: [1] $[Fe(en)_3]^{2+}$: $\mu = \sim 5{\cdot}0$ B.M. (Kanekar and Nyholm, unpublished). [2] $[Co(en)_3]^{2+}$: $\mu = 4{\cdot}9$ B.M. (*idem*; Mellow and Goldacre, *Proc. Roy. Soc. N.S.W.*, 1940, **73**, 233, reported $\mu = 3{\cdot}8$ B.M.). [3] $[Ni(en)_3]^{2+}$: $\mu = 3{\cdot}0$—$3{\cdot}2$ B.M. (Cambi, Cagnasso, and Tremolada, *Gazzetta*, 1934, **64**, 758; Cambi and Tremolada, *ibid.*, 1935, **65**, 322; Field and Vosburgh, *J. Amer. Chem. Soc.*, 1949, **71**, 2398). [4] This paper, p. 3575. [5] $[Fe(NO_2)_6]^{4-}$: $\mu = 0{\cdot}9$ B.M. (Asmussen, *Z. anorg. Chem.*, 1934, **218**, 425). [6] $[Co(NO_2)_6]^{4-}$: $\mu = 1{\cdot}9$ B.M. (Cambi and Ferrari, *Gazzetta*, 1935, **65**, 1162). $[Ni(NO_2)_6]^{4-}$: $\mu = 3{\cdot}1$ B.M. (*idem*, *ibid.*).

EXPERIMENTAL

The following preparations are reported in some detail only when the compounds are new or where modifications have been made to the original method of isolation.

Tris-2 : 2′-*dipyridylchromium*(II) *Dibromide Tetrahydrate*.—Freshly prepared chromous acetate (10 g.) was treated with air-free hydrobromic acid (constant-boiling; 30 ml.), previously just decolorised by boiling it with a few drops of hypophosphorous acid, in a stream of carbon dioxide. The flask was cooled in ice, and the blue precipitate of chromous bromide washed twice with small quantities of ice-cold air-free distilled water. Dipyridyl (1·0 g.), dissolved in water (10 ml.) containing 10N-hydrochloric acid (4 drops), was then added to the chromous bromide, followed by a large excess of solid sodium bromide. The black crystalline complex was precipitated instantly, and this was filtered off after cooling at 0° in carbon dioxide for ½ hour. The compound (0·9 g.) was washed twice with ice-cold distilled water and once with alcohol, and then dried in a partly evacuated desiccator over calcium chloride, the tetrahydrate being formed (Found: C, 47·25; H, 4·6; N, 11·0; Br, 21·0; Cr, 6·7. Calc. for $C_{30}H_{24}N_6Br_2Cr,4H_2O$: C, 47·7; H, 4·25; N, 11·15; Br, 21·3; Cr, 6·9%). The compound was stored under carbon dioxide. Although stable in dry air, it was oxidised rapidly in aqueous solution, the colour changing from dark brown to yellow.

Tris-2 : 2′-*dipyridylchromium*(III) *Perchlorate*.—This salt was made from the foregoing bromide by shaking it with aqueous 5% perchloric acid in air; the yellow deposit was separated and crystallised from warm water (Found: Cr, 6·4; N, 10·1. Calc. for $C_{30}H_{24}O_{12}N_6Cl_3Cr$: Cr, 6·35; N, 10·3%).

Bis-2 : 2′-*dipyridyldichlorochromium*(III) *Chloride Dihydrate*.—Anhydrous chromic chloride (1·5 g.) and 2 : 2′-dipyridyl (4·7 g.) in alcohol (50 ml.) were mixed and heated to boiling after addition of a trace of zinc dust as catalyst. A vigorous reaction took place, the chromic chloride dissolving to a deep brown solution. The mixture was kept at the b. p. for ten minutes and then allowed to cool; dark red-brown crystals separated and were filtered off and dissolved in a small quantity of hot water. This solution was filtered and allowed to crystallise; the complex *chloride* separated as dark brown crystals which were air-dried (Found: C, 48·1; H, 4·27; N, 10·9; Cr, 10·6; H_2O, 7·4. $C_{20}H_{16}N_4Cl_3Cr,2H_2O$ requires C, 47·5; H, 3·95; N, 11·05; Cr, 10·3; H_2O, 7·35%).

Tris-2 : 2′-*dipyridylmanganese*(II) *Bromide*.—Manganous sulphate tetrahydrate (2·2 g.)

was dissolved in water (10 ml.) and treated with 2 : 2′-dipyridyl (4·7 g.), and the mixture heated and stirred until the base dissolved. A few drops of alcohol were added to assist solution of the last traces of diamine. The yellow solution was then filtered and cooled, and a solution of potassium bromide (10 g.) in water (50 ml.) added; a yellow microcrystalline precipitate separated. The complex *bromide* was filtered off, recrystallised from hot water, and air-dried (Found: C, 52·7; H, 3·5; N, 12·3; Mn, 7·9. $C_{30}H_{24}N_6Br_2Mn$ requires C, 52·4; H, 3·8; N, 11·4; Mn, 8·0%).

Tris-2 : 2′-*dipyridylferrous Perchlorate*.—2 : 2′-Dipyridyl (2·0 g.), dissolved in hot distilled water (300 ml.), was treated with excess of ferrous sulphate and sodium perchlorate solution. The red solution was heated on the water-bath for one hour and then left to cool. The red crystalline perchlorate (3·3 g.) which separated was filtered off, well washed with distilled water, and dried *in vacuo* (Found: C, 49·8; H, 3·4; N, 11·5. Calc. for $C_{30}H_{24}O_8N_6Cl_2Fe$: C, 49·7; H, 3·3; N, 11·6%).

Tris-2 : 2′-*dipyridylferric Perchlorate Trihydrate*.—Ferrous sulphate heptahydrate (1·0 g.) in distilled water (70 ml.) was treated with 36N-sulphuric acid (0·2 ml.) and 2 : 2′-dipyridyl (1·5 g.), and the blood-red solution filtered. The ice-cold solution was saturated with chlorine and warmed to room temperature, a deep blue colour developing. More chlorine was passed in to ensure complete oxidation and excess of 30% sodium perchlorate solution was then added, and the solution allowed to cool in ice. Blue-green crystals of the *perchlorate* were formed; these (1·3 g.) were filtered off, well washed with distilled water, and dried *in vacuo*. In sunlight the compound gradually became red (Found: C, 41·0; H, 4·0; N, 9·2. $C_{30}H_{24}O_{12}N_6Cl_3Fe,3H_2O$ requires C, 41·1; H, 3·4; N, 9·6%).

Tris-2 : 2′-*dipyridylcobalt*(II) *Perchlorate*.—A solution of cobaltous chloride hexahydrate (0·6 g.) in alcohol (25 ml.) was filtered, boiled to remove air, and treated with dipyridyl (1·2 g.) in hot alcohol (20 ml.), the solution becoming brown. Carbon dioxide was passed into the mixture, which was then diluted with air-free distilled water (50 ml.), and excess of sodium perchlorate was added. After 15 minutes in ice, the salt was filtered off, well washed with distilled water, and dried *in vacuo* (Found: C, 50·2; H, 3·6; N, 10·9. Calc. for $C_{30}H_{24}O_8N_6Cl_2Co$: C, 49·6; H, 3·3; N, 11·5%).

Tris-2 : 2′-*dipyridylcobalt*(III) *Perchlorate Trihydrate*.—Cobaltous chloride hexahydrate (2·4 g.) and 2 : 2′-dipyridyl (4·7 g.) were heated with distilled water (50 ml.) until complete solution had occurred. The yellow solution was treated with hydrogen peroxide (10 ml.; 30%) and hydrochloric acid (10 ml.; *d* 1·18), and the mixture evaporated to a syrupy consistency. Water (50 ml.) was then added, and the solution treated with perchloric acid (10 ml.; 60%), the yellow crystalline perchlorate then separating. This was recrystallised from hot water and air-dried (Found: C, 41·0; H, 3·4; N, 9·55; Co, 6·6; H_2O, loss at 110°, 5·2. Calc. for $C_{30}H_{24}O_{12}N_6Cl_3Co,3H_2O$: C, 41·1; H, 3·5; N, 9·5; Co, 6·7; H_2O, 6·1%).

Tris-o-*phenylenebisdimethylarsinecobalt*(II) *Perchlorate*.—Anhydrous cobaltous acetate (0·3 g.) was dissolved in aqueous alcohol (1 : 1; 20 ml.) containing 17N-acetic acid (2 drops), and the hot solution filtered. After being boiled free from air, the solution was treated with the ditertiary arsine (0·8 g.) dissolved in air-free alcohol, and evaporated *in vacuo* (Found: C, 32·3; H, 4·3%). $C_{30}H_{48}O_8As_6Cl_2Co$ requires C, 32·3; H, 4·3%). The substance is insoluble in water but is moderately soluble in nitrobenzene, nitromethane, and benzonitrile.

Tris-o-*phenylenebisdimethylarsinecobalt*(III) *Perchlorate*.—Cobaltous acetate (0·2 g.) in distilled water (15 ml.) containing 17N-acetic acid (3 drops) was treated with the ditertiary arsine (0·8 g.) in absolute alcohol (30 ml.). The brown solution was heated to boiling and then freely exposed to the air for 23 hours, during which the brown solution became yellow. Excess of perchloric acid (60%, 5 ml.) was then added, and the solution heated on the water-bath. After a few seconds the microcrystalline yellow *perchlorate* separated; it (0·8 g.) was filtered off, well washed with water and alcohol, and dried in *vacuo* (Found: C, 29·4; H, 3·8. $C_{30}H_{48}O_{12}Cl_3As_6Co$ requires C, 29·6; H, 3·95%). The compound has solubilities similar to those of the corresponding cobaltous complex.

Di-o-*phenylenebisdimethylarsinediacetatocobalt*(III) *Perchlorate*.—This *salt* was prepared in exactly the same way as the preceding compound, except that a deficiency of the arsine was used and a large excess of acetic acid added. After being left for 24 hours the solution had a reddish-pink colour. Excess of perchloric acid followed by distilled water was added, and a red precipitate was formed. This was recrystallised from hot water containing a trace of acetic acid, glistening red crystals being obtained (Found: C, 34·0; H, 4·6. $C_{24}H_{38}O_8ClAs_4Co$ requires C, 34·0; H, 4·5%).

Tris-2 : 2′-*dipyridylnickel*(II) *Iodide Hexahydrate*.—Prepared according to Morgan and

Burstall (*J.*, 1931, 2213), the compound was obtained as a pink crystalline powder (Found : C, 40·9; H, 4·1; N, 8·9. Calc. for $C_{30}H_{24}N_6I_2Ni,6H_2O$: C, 40·6; H, 4·1, N, 9·4%).

Tris-2 : 2′-*dipyridylnickel*(II) *Perchlorate*.—Prepared as for the iodide, this was obtained as a pink crystalline powder (Found : C, 49·4; H, 3·5; N, 11·4; Ni, 8·0. Calc. for $C_{30}H_{24}O_8N_6Cl_2Ni$: C, 49·6; H, 3·3; N, 11·6; Ni, 8·1%).

Reaction of Chromic Chloride with the Ditertiary Arsine.—Chromic chloride tetrahydrate (0·6 g.), dissolved in alcohol (10 ml.), was treated with the ditertiary arsine (1·2 g.) (Cr : diarsine = 1 : 2), dissolved in alcohol (15 ml.), and the green solution heated to boiling. A blue colour gradually appeared and this deepened when the solution was left for 48 hours. Most of the alcohol was evaporated off on the water-bath, the residue dissolved in chloroform and filtered, and the filtrate treated with light petroleum, a sticky blue precipitate being formed. This was recrystallised twice from a chloroform and light petroleum, the first greenish fraction being rejected on each occasion. A beautiful blue powder was obtained. Analysis indicated that the compound $[CrCl_2(Diarsine)(EtOH)(H_2O)]Cl$ was impure, but in nitrobenzene the molar conductivity (0·8 mho at $c = 3 \times 10^{-3}$M) indicates that the substance is almost a non-electrolyte. The compound is readily soluble in alcohol, acetone, nitrobenzene, chloroform, and nitromethane, but not in benzene or light petroleum, and dissolves in water only with decomposition. It reacts readily with aqueous silver nitrate solution to give a white precipitate. The gram-susceptibility ($\chi_g = 11·3 \times 10^{-6}$) led to $\mu = \sim 3·9$ B.M.

Magnetic-susceptibility Measurements.—The Gouy method was employed, the balance described by Baddar, Hilal, and Sugden (*J.*, 1949, 132) being used.

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682. *Studies in Co-ordination Chemistry. Part XIV.* The Magneto-chemistry of Simple and Complex Fluorides of Transition Metals.*

By R. S. NYHOLM and A. G. SHARPE.

The magnetic susceptibilities of the following compounds at 20° are reported for the first time: K_2TiF_6; K_2TiF_6,H_2O; VF_3; K_3VF_6; K_2CrF_5,H_2O; $KCrOF_4$; K_2MnF_5,H_2O; Li_3FeF_6; Na_3FeF_6; K_2FeF_5; $CsFeF_4$; $CuF_2,2H_2O$; TaF_3; RhF_4; Na_3RhF_7; PdF_3; PtF_4; K_2PtF_6; AuF_3; $AgAuF_4$. The susceptibilities of several other transition-metal fluorides have been redetermined and available data for all fluorine-containing transition-metal compounds have been assembled. The correlation of the observed magnetic moments with valency, structural chemistry, and bond type is discussed. Compounds of the first transition series, except when magnetically concentrated, show the number of unpaired electrons calculated for so-called "ionic" bonds on the assumption of maximum multiplicity. For the second and third transition series the compounds are diamagnetic when the number of electrons in the metal ion is even and paramagnetic, with a moment corresponding to only one unpaired electron, when the number of electrons is odd, showing that for these two series minimum multiplicity is the rule even for fluorides. Possible reasons for these observations are discussed.

IN the development of the structural chemistry of transition-metal compounds, fluorides have occupied an important position, since the difference in magnetic properties between the strongly paramagnetic complex ions, such as $[FeF_6]^{3-}$ and $[Fe(H_2O)_6]^{3+}$, and the weakly paramagnetic complex ions, such as $[Fe(CN)_6]^{3-}$, is the key point in the division

* Part XIII, preceding paper.

of bonds in ferric complexes into two types. The nature of these two types of binding has been much discussed, *e.g.*, by Pauling (*J. Amer. Chem. Soc.*, 1931, **53**, 1367; "Nature of the Chemical Bond," Cornell Univ. Press, 1939), Van Vleck ("Theory of Electric and Magnetic Susceptibilities," Oxford Univ. Press, 1932; *J. Chem. Phys.*, 1935, **3**, 807), Selwood ("Magnetochemistry," Interscience Publ. Corp., N.Y., 1943), Asmussen ("Magnetokemiske Undersøgelser over Uorganiske Kompleksforbindelser," Copenhagen, 1944), and Burstall and Nyholm (Part XIII*). Here we adopt the view taken in Part XIII, that for octahedral bonds the essential distinction is between the use of $3d^2 4s 4p^3$ hybrid orbitals ("covalent" bonds in Pauling's terminology) and $4s 4p^3 4d^2$ hybrid orbitals ("ionic" bonds in Pauling's terminology). A more detailed theoretical discussion of the use of higher (4*d*) orbitals for σ- and π-bond formation in transition-metal complexes occurs in a forthcoming publication by Craig, Maccoll, Nyholm, Orgel, and Sutton (see also Orgel, *Nature*, 1951, **167**, 434).

It is well known that, in the first transition series, the more electronegative ligands (such as F, Cl, O) favour the use of higher orbitals, giving compounds with the maximum magnetic moments, whereas ligands containing atoms of lower electronegativity (*e.g.*, P, As, S) generally favour the use of lower-level bonding orbitals with maximum electron pairing. The fluorides of transition metals are especially interesting, since fluorine is particularly effective in producing higher oxidation states [*e.g.*, Co(IV), Ni(IV), Cu(III)] and in forming compounds with the most polar bonds. There is thus a greater likelihood of the metal being present as an ion, and maximum magnetic moments are therefore more likely to be found in fluorides than in any other compounds.

The comparative inaccessibility and instability of many fluorine-containing compounds have hitherto limited the range of such substances examined, and no general account of their magnetic properties is available. In the present investigation susceptibilities have been measured at or near 20° and the values corrected to this temperature, on the assumption that the Curie law is valid. The fact that the simple Curie law is not strictly obeyed by many, if not by most, substances is unimportant for this small correction, since temperature differences were only of the order of $\pm 5°$. The effect of wide variation in temperature or field strength has not been studied, but the mere demonstration of the presence or absence of unpaired electrons is often of great interest. It is intended to examine the magnetic behaviour of certain of the more magnetically concentrated compounds in more detail, with a view to determining values of Δ in the Curie–Weiss expression [molar susceptibility $\propto \propto 1/(T + \Delta)$] and hence obtaining moments calculated on the basis of this Law. For many compounds of transition metals, Δ is large and, though μ is proportional only to $\sqrt{T + \Delta}$, we are not justified in discussing in this paper small differences between values of μ calculated on the Curie law and values for other compounds calculated on the Curie–Weiss law. This limitation of our general survey of moments at 20° has been stressed throughout the following discussion. Van Vleck (*op. cit.*, p. 304) has discussed the theoretical significance of Δ; since Δ is usually smaller in magnetically dilute compounds, it is suggested that exchange forces between paramagnetic atoms are at least partly responsible for it. However, the view that Δ is often due mainly to the influence of orbital angular momentum finds support in the fact that Δ is usually smaller for Mn(II) and Fe(III) salts that for most others; in these cases we are of course dealing with *S* states where the total orbital angular momentum is zero.

The purity of all samples has been checked by at least partial analysis for the essential constituents. Corrections have been made for atomic diamagnetism (except that of the paramagnetic atom itself) in all instances. Except where special mention is made in the Experimental section (*e.g.*, for CoF_3) no paramagnetic corrections for impurities have been made. Previous work (*e.g.*, Woolf and Emeléus, *J.*, 1949, 2865; Sharpe, *J.*, 1950, 3444) has shown that, although substances prepared in bromine trifluoride are seldom quite pure, the degree of impurity is not such as would appreciably affect the values quoted for the magnetic moments. The importance in this work of analysis for a sufficient number of elements to justify the magnetic moment claimed is all too frequently overlooked, and for that reason any moments which are reported in the literature without a satisfactory accompanying analysis should be accepted with reserve.

The results of the experimental work in this investigation are given in Table 1; all values for μ are believed to be accurate to within $\pm 0{\cdot}1$ B.M. or less. In Table 2 are shown all the moments of the transition-metal fluorides which have so far been reported. Owing

TABLE 1.

	Compound	$\chi_g^{20°}$, $\times 10^{-6}$	$\chi_M^{20°}$, $\times 10^{-6}$	Diamagnetic corrn., $\times 10^{-6}$	$\chi_M^{20°}$, $\times 10^{-6}$ (corr.).	μ
1	K_2TiF_6	−0·28				Diamagnetic
2	K_2TiF_6,H_2O	−0·18				Diamagnetic
3	VF_3	2·53	2,730	27	2,757	2·55
4	K_2VF_6	11·3	3,200	99	3,300	2·79
5	K_2CrF_5,H_2O	24·6	5,980	86	6,066	3·79
6	$KCrOF_4$	6·90	1,262	46	1,308	1·76
7	MnF_3	91·4	10,240	27	10,270	4·94
8	K_2MnF_5,H_2O	18·6	4,575	86	4,661	3·32
9	Li_3FeF_6	75·2	14,400	58	14,460	5·87
10	Na_3FeF_6	62·5	14,920	75	14,995	5·95
11	$(NH_4)_2FeF_6$	63·3	14,180	94	14,274	5·80
12	K_2FeF_5	43·9	10,020	76	10,100	4·87
13	$CsFeF_4$	36·0	9,680	91	9,770	4·79
14	CoF_3	16·4	1,900	27	1,927	2·1
15	$CuF_2,2H_2O$	11·35	1,560	39	1,600	1·94
16	TaF_3	3·3	795	27	822	1·4
17	RhF_4	2·8	500	36	536	1·1
18	Na_2RhF_7	3·92	1,195	84	1,279	1·74
19	PdF_3	10·8	1,760	27	1,787	2·05
20	PtF_4	1·68	455	36	491	1·1
21	K_2PtF_6	−0·21				Diamagnetic
22	AuF_3	0·30	74	27	101	0·5
23	$AgAuF_4$	—				Diamagnetic

partly to their greater ease of preparation and partly to the greater interest previously attaching to them, results for fluorides of metals of the first transition series are more numerous than for the other two. It is convenient to discuss the results for individual elements in turn before arriving at some more general conclusions.

The diamagnetism of potassium fluorotitanate, thorium tetrafluoride, potassium hexafluorotantalate, and the hexafluorides of molybdenum, tungsten, and uranium is expected and calls for no special comment. The values for europous fluoride, and for uranium tetrafluoride and plutonium trifluoride, have been discussed by Selwood (*loc. cit.*) and Dawson (*loc. cit.*) respectively. For tantalum trifluoride the observed moment of 1·4 B.M. is far below that expected for a Ta^{3+} ion if maximum multiplicity were operative; then the moment should be similar to that of the V^{3+} ion; the environment of the Ta^{3+} ion in TaF_3 (Jack and Gutmann, *Acta Cryst.*, 1951, **4**, 244) differs little from that of the V^{3+} ion in VF_3 (*idem*, *ibid.*, p. 246), but, since magnetic measurements have been made only at 20° and no data are available for other compounds of lower oxidation states of tantalum, it is difficult to make any deduction from this result. The following discussion is therefore restricted to elements in the first transition series, the platinum metals, silver, and gold.

Vanadium.—Only compounds of the tervalent state are available for study and for all of these except VF_3 the moment is close to that calculated for the spin-only value for two unpaired electrons (2·83 B.M.). The moment of VF_3 is noticeably lower than that calculated for VCl_3 from the Curie–Weiss law [2·85 B.M. (Starr, Bitter, and Kaufman, *Phys. Review*, 1940, **58**, 977; Starr, *ibid.*, p. 984)]; presumably this is caused by the magnetic concentration, but in the absence of data for various temperatures calculation of Δ and application of the Curie–Weiss law are not possible. For vanadium alum between 3° K and 293° K it has been shown by Handel and Siegert (*Physica*, 1937, **4**, 871) that the Weiss law is obeyed, μ being 2·62 B.M. It should be mentioned that, since a V^{3+} ion contains only two 3*d* electrons (both unpaired), there are three vacant 3*d* orbitals available for bond formation. Magnetic moments would therefore provide no basis for distinguishing between "ionic" and "covalent" bonds, since both types of binding would give the same moment (Pauling, *op. cit.*). When two 3*d* orbitals are available without promotion of

TABLE 2. *Magnetic moments at 20° (ref. in parentheses).*

	K_2TiF_6 0·0 (1)	VF_3 2·55 (1)	CrF_3 3·9 (3)	MnF_2 5·73 (4, 11)	FeF_2 5·59 (6)	CoF_2 4·60 (8, 10)	NiF_2 2·85 (8, 11)	CuF_2 1·57 (8, 11)
	K_2TiF_6,H_2O 0·0 (1)	K_2VF_6 2·79 (1)	K_2CrF_5,H_2O 3·79 (1)	MnF_3 4·94 (1) 4·91 (21)	FeF_3 — (4)	CoF_3 2·46 (8) 2·1 (1)		
		$(NH_4)_2VF_6$ 2·79 (2)		K_2MnF_5,H_2O 3·32 (1)	Li_3FeF_6 5·87 (1)		K_2NiF_6 0·0 (9)	$CuF_2,2H_2O$ 1·94 (1)
		K_2VF_5,H_2O 2·74 (2)	$KCrOF_4$ 1·76 (1)		Na_3FeF_6 5·95 (1)	K_2CoF_6 4·26 (5)		
		$(NH_4)VF_4,2H_2O$ 2·77 (2)		K_2MnF_6 3·86 (5)	$(NH_4)_2FeF_6$ 5·88 (7) 5·80 (1)	$Co(NH_3)_6F_3$ 0·0 (2)		K_2CuF_6 2·8 (9)
		$VF_3,3H_2O$ 2·79 (2)			K_2FeF_5 4·87 (1)	$Co(NH_3)_3F_3$ 0·0 (19)		
					$(NH_4)_2FeF_5,H_2O$ 5·91 (7)			
					$FeF_3,3H_2O$ 4·25 (7)			
					$CsFeF_4$ 4·79 (1)			
			MoF_6 0·0 (12)			RhF_4 1·1 (1)	PdF_2 2·05 (1)	AgF_2 1·0 (17, 18)
						Na_2RhF_7 1·74 (1)		
EuF_3 7·4 (15)		TaF_5 1·4 (1)	WF_6 0·0 (12)				PtF_4 1·1 (1)	AuF_3 0·5 (1)
		$KTaF_6$ 0·0 (16)					K_2PtF_6 0·0 (1, 20)	$AgAuF_4$ 0·0 (1)
	ThF_4 0·0 (13)		UF_4 2·92 (13)					
			UF_6 0·0 (12)					
			PuF_3 1·25 (14)					

(1) Present work. (2) Asmussen, *loc. cit.* (3) Bizette and Tsai, *Compt. rend.*, 1940, **211**, 252. (4) *Idem, ibid.*, 1939, **209**, 205. (5) Grey, *J. Amer. Chem. Soc.*, 1946, **68**, 605. (6) Bizette and Tsai, *Compt. rend.*, 1941, **212**, 119. (7) Feytis, *ibid.*, 1911, **152**, 710. (8) Henkel and Klemm, *Z. anorg. Chem.*, 1935, **222**, 73. (9) Klemm, personal communication; Hoppe, *Angew. Chem.*, 1950, **62**, 339. (10) de Haas, Schultz, and Koothaus, *Physica*, 1939, **6**, 481. (11) *Idem, ibid.*, 1940, **7**, 57. (12) Henkel and Klemm, *Z. anorg. Chem.*, 1935, **222**, 70. (13) Dawson, *J.*, 1951, 2889; 1952, 1185. (14) Dawson, Mandleberg, and Davies, *J.*, 1951, 2047. (15) Klemm and Döll, *Z. anorg. Chem.*, 1939, **241**, 233. (16) Bose and Bhar, *Z. Physik*, 1928, **48**, 716. (17) Ruff, Giese, and Hartmann, *Z. anorg. Chem.*, 1934, **219**, 146. (18) Gruner and Klemm, *Naturwiss.*, 1937, **25**, 59. (19) Cartledge, quoted by Pauling, *loc. cit.*, p. 117. (20) D. P. Mellor, personal communication. (21) Klemm and Krose, *Z. anorg. Chem.*, 1947, **253**, 226.

electrons, however, it is difficult to find any justification for suggesting the use of 4*d* orbitals for hybrid-bond formation; that all compounds of V(III), Cr(III), and Mn(IV) should show similar magnetic properties then follows as a matter of course.

Chromium.—Bizette and Tsai (*loc. cit.*) give μ 3·9 at 20° for CrF_3 (calculated from their graph); Starr, Bitter, and Kaufman (*loc. cit.*) and Starr (*loc. cit.*) report the same value for $CrCl_3$ at 25°. Tervalent chromium with configuration d^3 has two vacant 3*d* orbitals and the binding is probably $3d^24s4p^3$, since there is no reason to suppose otherwise. The complex K_2CrF_5,H_2O, like all other tervalent chromium complexes, has a moment corresponding well with three unpaired electrons.

The moment of $KCrOF_4$ corresponds closely with one unpaired electron and is analogous to those of Rb_2CrOCl_5 (μ = 1·80 B.M.) and Cs_2CrOCl_5 (μ = 1·84 B.M.), both results being reported by Asmussen (*loc. cit.*); this is the moment expected for Cr(V). The crystal structure is unknown and there is at present no evidence for discrete $CrOF_4^-$ ions.

Manganese.—(*a*) Mn(II). Like manganous chloride (Starr, Bitter, and Kaufman, *loc. cit.*; Starr, *loc. cit.*), manganous sulphate (Asmussen, *loc. cit.*), and many complexes of Mn(II), MnF_2 has approximately the value of μ for 5 unpaired electrons. Only the complex cyanide $K_4Mn(CN)_6,3H_2O$, for which Asmussen (*loc. cit.*) reports 2·13 B.M. (see also Goldenberg, *Trans. Faraday Soc.*, 1940, **36**, 847) differs from this. The reluctance of Mn(II) to form complexes in which electron pairing occurs is very well known; possible reasons for this have been discussed in Part XIII.

(*b*) Mn(III). The moment of MnF_3 is in reasonable agreement with that calculated for four unpaired electrons. This is the only stable anhydrous salt of tervalent manganese, but many complexes are known for which μ is 4·9—5·0 B.M. These presumably utilise higher octahedral $4s4p^34d^2$ orbitals. For the tervalent complex cyanide $K_3Mn(CN)_6$ moments of 3·18 B.M. (Asmussen, *loc. cit.*) and 3·64 B.M. (Biltz, *Z. anorg. Chem.*, 1928, **170**, 161) are reported; as in the bivalent complex cyanide, the binding is clearly $3d^24s4p^3$, there being two unpaired electrons. The difference between the experimental results of the two workers is serious but does not affect this conclusion. We have observed a reduction of moment with K_2MnF_5,H_2O which is entirely unexpected and this compound is being further investigated. Goldenberg (*loc. cit.*) reports μ 0·6 B.M. for a compound which he tentatively formulated as $K_3Mn_2(CN)_9,4KOH$, but his analytical data for both Mn and CN differ considerably from the calculated figures and no evidence for the KOH is quoted in the paper. Until the formula is more satisfactorily established the moment cannot be interpreted.

(*c*) Mn(IV). Grey (*loc. cit.*) reports μ 3·86 for K_2MnF_6, in good agreement with the spin-only value for three unpaired electrons, but again the magnetic data are not diagnostic of the bond type. Similar values are quoted by Asmussen (*loc. cit.*) for many other quadrivalent manganese compounds. For the complex $KMnF_5$ (which cannot be obtained pure) we found μ 4·3 B.M. This value is rather higher than the spin-only value and even some contamination with Mn(III) would not completely account for the high moment. The structure of this salt is unknown and the excess in the moment may arise from an incompletely quenched orbital contribution.

Iron.—(*a*) Fe(II). The value for FeF_2 is close to that of $FeCl_2$, for which μ is 5·59 B.M. (Starr, Bitter, and Kaufman, *loc. cit.*); the values for magnetically dilute ferrous compounds range from 5·0 to 5·6 B.M. [*e.g.*, $FeSO_4,(NH_4)_2SO_4,6H_2O$ has μ 5·55 B.M.] The behaviour is thus characteristic of the Fe^{2+} ion and must, as with bivalent cobalt complexes, arise from a large orbital contribution.

(*b*) Fe(III). Ferric fluoride shows field strength dependence at both 20° and −183°; hence moments are meaningless. The moments of several complex fluoroferrates have been measured at 20° and these yield interesting results. Some slight indication of field strength dependence was obtained for the more concentrated compounds, but of greater interest is the departure from the spin-only value (observed with the hexafluoroferrates) when tetra- and penta-fluoroferrates are formed. As the size of the alkali metal cation increases, the atomic ratio F : Fe decreases and a decrease in moment is observed. This decrease in moment as the magnetic concentration increases is most interesting and it is proposed to follow this problem by an investigation of crystal structures of complexes

such as K_2FeF_5 and $CsFeF_4$ and of their variation of magnetic susceptibility with temperature. We have discarded the value of μ 5·2 B.M. for Na_3FeF_6 reported by Welo (*Phil. Mag.*, 1928, **6**, 496) since his analytical figures do not agree with the above formula.

Cobalt.—(*a*) Co(II). The moment of CoF_2 (4·60 B.M.) is much higher than that calculated for three unpaired electrons, but this behaviour is quite general for compounds of bivalent cobalt. The value of μ generally increases as we pass from tetrahedral to octahedral Co(II) complexes owing to the greater contribution to the moment. This experimental observation covering a wide range of compounds (Kanekar and Nyholm, unpublished work) can be predicted theoretically from calculations on the effect of various crystalline fields on the size of the moment (Bose, *Indian J. Phys.*, 1948, **22**, 76, 195, 483, and earlier references quoted therein). The value of the orbital contribution in tetrahedral complexes is also quite sensitive to changes in the electronegativity of the attached groups. Calculated on the Curie law, the value of μ for CoF_2 increases steadily with temperature from 90° K to 293° K (Henkel and Klemm, *loc. cit.*) and the figure quoted for 20° C has therefore probably not reached its limiting value. Since Δ is not constant it is impossible to calculate the value of μ from the Curie–Weiss law.

(*b*) Co(III). The value reported by Henkel and Klemm for CoF_3 has been confirmed. For this compound there is also temperature dependence at least up to 293° K, but the Curie–Weiss law is not obeyed, and hence the limiting value of μ is certainly greater than 2·5 B.M. According to Gutmann and Jack (*loc. cit.*), CoF_3 is probably isomorphous with VF_3, each cobalt atom having six octahedrally arranged fluorine atoms as nearest neighbours. Tervalent cobalt is d^6; if the bonds were $3d^24s4p^3$ the complexes would be diamagnetic (as in the complex ammines) but the use of "ionic" or $4s4p^34d^2$ bonds with maximum multiplicity requires a moment of 4·90 B.M., there being four unpaired electrons. The value reported by Grey (*loc. cit.*) for the blue complex salt K_3CoF_6, which was prepared by Mitchell (Thesis, Univ. Buffalo, 1940) by treating $Co_2F_6,7H_2O$ with potassium fluoride in aqueous hydrofluoric acid, is rather less than this, but it certainly shows that the binding is not $3d^24s4p^3$ and is more consistent with $4s4p^34d^2$ hybrid orbitals. This fluoride thus differs from all other Co(III) complex ions, including even the $Co(H_2O)_6^{2+}$ ion, for which Asmussen (*loc. cit.*) and Barkworth (Thesis, London, 1937) report $\mu < 0{\cdot}5$ B.M. (even this small moment is probably due to traces of cobaltous salt). Thus, with the exception of the compounds K_3CoF_6 and $CoCl_3,2Et_3P$ (Jensen, unpublished work) for both of which μ indicates four unpaired electrons, tervalent cobalt in its complex compounds resembles metals of the second and third transition series much more than those of the first.

Nickel.—(*a*) Ni(II). The moment of NiF_2 is also temperature dependent from 90° K to 293° K (Henkel and Klemm, *loc. cit.*); the value at 293° K corresponds to two unpaired electrons. Since, however, Ni(II) compounds usually have moments of the order of 3·1—3·3 B.M. it seems that some reduction of moment owing to magnetic concentration has occurred.

(*b*) Ni(IV). The complex K_2NiF_6 is of great interest as showing a resemblance between nickel in its highest valency state and the platinum metals (cf. K_2PtF_6). Diamagnetism in the Ni(IV) complex, $[NiCl_2(diarsine)_2][ClO_4]_2$ (Part IX, *J.*, 1951, 2602), is not surprising, since the ditertiary arsine is a donor of low electronegativity and favours the use of the 3*d* orbitals for binding. The failure to observe paramagnetism in K_2NiF_6, however, shows that Ni(IV) in its complex fluoride has even greater capacity for covalent bond formation using $3d^24s4p^3$ orbitals than the isoelectronic Co(III).

Copper.—(*a*) Cu(II). No complex fluoride is known. The structure of $CuF_2,2H_2O$ is unknown but if it is similar to that of $CuCl_2,2H_2O$ the four bonds are co-planar. This requires dsp^2 bonds; these might be $3d4s4p^2$, involving the promotion of an electron to a higher (4*p*) orbital, or, more probably, $4s4p^24d$ orbitals as originally suggested by Huggins (*J. Chem. Phys.*, 1937, **5**, 527). Strong support for the latter view is found on theoretical grounds (Craig, Maccoll, Nyholm, Orgel, and Sutton, unpublished work) and it overcomes the objection that if an electron is promoted its removal by oxidation should be facilitated. Such ready oxidation of square Cu(II) complexes is, of course, not observed.

(*b*) Cu(III). The moment of K_3CuF_6 indicates two unpaired electrons; the use of $3d^24s4p^3$ orbitals would necessitate the most improbable promotion of two unpaired

electrons, but the use of $4s4p^34d^2$ hybrid orbitals leaves these two unpaired electrons in the $3d$ shell. This makes the reasonable assumption that the CuF_6^{3-} ion is octahedral.

Silver.—The moment of AgF_2 is notably low in comparison with those of Ag(II) complexes, which have values of μ corresponding closely with that required for one unpaired electron. The reason for this is as yet unknown.

The Platinum Metals.—These elements are noted for their tendency to form diamagnetic complexes, but paramagnetism has been reported in a few instances. Ruthenium trichloride (Cabrera and Fahlenbrach, *Anal. Fis. Quim.*, 1934, **32**, 1045; *Ann. Physik*, 1934, **21**, 832) has μ 2·09 B.M., and similar values are reported for many Ru(III) complexes (Gleu and Breuel, *Z. anorg. Chem.*, 1938, **237**, 326, 335, 350). For K_2RuCl_6, μ is 2·83 B.M. (Groves, Thesis, London, 1941); here there are clearly two unpaired electrons as required for $4d^25s5p^3$ octahedral orbitals. Groves also reported μ 1·4 B.M., an unexpectedly low value, for K_2OsCl_6. For Ir(IV), isoelectronic with Ru(III), Bose and Bhar (*Z. Physik*, 1928, **48**, 716) gave μ 1·9 B.M. for $IrCl_4$. Whether or not Hund's maximum multiplicity principle is generally valid, paramagnetism is, of course, to be expected in any compound in which the number of electrons on the metal is odd, *e.g.*, for compounds of Ru(III), Os(III), Rh(II), Rh(IV), Ir(II), Ir(IV), Pd(III), and Pt(III).

The complex Na_3RhF_7 is the first rhodium compound to show the moment required for one unpaired electron. The moment for the magnetically more concentrated simple fluoride is smaller, but its temperature dependence has not been measured. Palladium trifluoride, like many Ni(III) complexes (NiF_3 has not been described), has a moment corresponding to a single unpaired electron; the physical characteristics of palladium trifluoride suggest an ionic structure, though previous claims for the isomorphism of PdF_3 and CoF_3 have been questioned by Gutmann and Jack (*loc. cit.*). The diamagnetism of both K_2NiF_6 and K_2PtF_6 is entirely in accord with the assumption that octahedral complexes using $3d^24s4p^3$ and $5d^26s6p^3$ bonds are formed. The octahedral arrangement of the PtF_6^{2-} ion has already been established by *X*-ray crystallography (Mellor and Stephenson, *Austral. J. Sci. Res.*, 1951, **4**, *A*, 406). It is also interesting to note that Lander (*Acta Cryst.*, 1951, **4**, 148) and Lander and Wooten (*J. Amer. Chem. Soc.*, 1951, **73**, 2452) have prepared the complex $BaNiO_3$ and have shown that the Ni(IV) atom is octahedrally co-ordinated, the very weak paramagnetism of this compound being attributed to a small amount of dissociation.

Finally, the moment of the gold complexes calls for comment. The small moment of AuF_3 may be ignored. In passing it should be mentioned that a value of χ_g for $AuCl_3$ of $+0{\cdot}43 \times 10^{-6}$ is quoted in "International Critical Tables;" this figure has been erroneously transcribed from Meyer (*Ann. Physik*, 1899, **69**, 236) and should read $-0{\cdot}43 \times 10^{-6}$. In its physical properties auric fluoride differs notably from the other halides of gold; if it contains an Au^{3+} ion, the configuration for which would be $5d^8$, all of the electrons must be paired. Structures based on AuF_4 or AuF_6 squares or octahedra are also possible, however, and at present the structure is unknown. For the AuF_4^- ion the diamagnetism is in complete accord with the formation of covalent $5d6s6p^2$ bonds with the square arrangement found throughout the stereochemistry of complexes of tervalent gold.

The most important conclusion from this survey is that the previously observed differences in magnetic behaviour between the first and the later transition series exist also amongst the fluorides. Although these compounds might reasonably be expected to be the most likely to show maximum spin, in no instance are moments observed in the later series as high as those of analogous compounds of elements in the first transition series. Three possible explanations are suggested by Van Vleck (*loc. cit.*): (*a*) that the Hund theory of maximum multiplicity is not obeyed; (*b*) that the reduction is due to magnetic concentration; and (*c*) that the ions are not monatomic, *i.e.*, that metal–metal bonds are formed. Of these, (*c*) is known to be incorrect for K_2PtF_6 and many complex chlorides of the platinum metals; (*b*) is doubtless important in certain cases (cf. Dawson, *loc. cit.*), but it cannot account for the observed diamagnetism of both magnetically concentrated and magnetically dilute compounds; and it appears that (*a*) is the most likely general explanation of the smaller moments observed with these heavier elements.

This review emphasises the need for further experimental investigations along three

main lines : the preparation of simple and complex fluorides of many of the heavier elements, especially those for which no values at all appear in Table 2; for many of the key substances mentioned, a thorough study of the temperature and field-strength dependence of susceptibility; more extensive *X*-ray crystallographic study of many of the substances mentioned, since until this is done interpretation of results is practically impossible. We are at present pursuing the second of these studies.

Experimental

Potassium Fluorotitanate.—The monohydrate, prepared from the iron-free dioxide according to Marchetti (*Z. anorg. Chem.*, 1895, **10**, 66), was dehydrated at 120°. Titanium was determined by decomposition with concentrated sulphuric acid and precipitation of the dioxide with ammonia (Found : Ti, 20·0. Calc. for K_2TiF_6 : Ti, 20·0%).

Vanadium Trifluoride.—This was prepared and analysed by Dr. V. Gutmann (Emeléus and Gutmann, *J.*, 1949, 2979). Another determination of vanadium was made by decomposition with sulphuric and nitric acids, reduction with sulphurous acid, and titration with permanganate (Found : V, 48·0. Calc. for VF_3 : V, 47·2%).

Potassium Hexafluorovanadate(III).—Vanadium pentoxide (5 g.) and potassium iodide (30 g.) were heated with hydrofluoric acid on a steam-bath until most of the liberated iodine had volatilised; after addition of a further 5 g. of potassium iodide (to ensure completion of reduction to tervalent vanadium), the green sparingly soluble deposit was washed with water, acetone, and ether. The *compound* was analysed as above (Found : V, 18·6. K_3VF_6 requires V, 18·4%).

Tantalum Trifluoride.—This was prepared and analysed by Dr. V. Gutmann (Emuléus and Gutmann, *J.*, 1950, 2115). In the absence of any knowledge of the determination of tervalent tantalum, the complete stability of the substance towards water appeared to guarantee its freedom from fluoride or oxyfluoride of Ta(V).

Potassium Pentafluorochromate(III) *Monohydrate.*—This was prepared according to Christensen (*J. pr. Chem.*, 1887, **35**, 161); chromium was determined iodometrically after oxidation to chromate by persulphate (Found : Cr, 21·6. Calc. for K_2CrF_5,H_2O : Cr, 21·4%).

Potassium Tetrafluoro-oxychromate(V).—Preparation and analysis were by Sharpe and Woolf's methods (*J.*, 1951, 798) (Found : Cr, 28·2. Calc. for $KCrOF_4$: Cr, 28·4%).

Manganese Trifluoride.—Preparation from manganous iodate and bromine trifluoride (Sharpe and Woolf, *loc. cit.*), followed by removal of the solvent at 220°, gave the purple-red trifluoride (Found : Mn, 50·0. Calc. for MnF_3 : Mn, 49·2%).

Potassium Pentafluoromanganite(IV).—The product from interaction of potassium permanganate and bromine trifluoride (Sharpe and Woolf, *loc. cit.*) was heated to constant weight at 180° and analysed as described previously (Found : Mn, 30·5; F, 46·8; Br, 1·8. Calc. for $KMnF_5$: Mn, 29·1; F, 50·2%).

Potassium Pentafluoromanganite(III) *Monohydrate.*—This compound, prepared according to Müller and Koppe (*Z. anorg. Chem.*, 1910, **68**, 160), was analysed by decomposition with sodium carbonate, ignition of the insoluble residue to Mn_3O_4, and precipitation of fluoride from the filtrate as calcium fluoride (Found : Mn, 22·4; F, 39·2. Calc. for K_2MnF_5,H_2O : Mn, 22·4; F, 38·6%).

Fluoroferrates.—Lithium, sodium, and ammonium hexafluoroferrate(III), potassium pentafluoroferrate(III), and *cæsium tetrafluoroferrate*(III) were obtained from mixtures of the metal chlorides and hydrofluoric acid. Iron was determined gravimetrically after decomposition of the complexes by hot concentrated sulphuric acid [Found, for the Li salt : Fe, 28·6. Calc. for Li_3FeF_6 : Fe, 29·2. Found, for the Na salt : Fe, 23·9. Calc. for Na_3FeF_6 : Fe, 23·5. Found, for the NH_4 salt : Fe, 25·5. Calc. for $(NH_4)_3FeF_6$: Fe, 25·0. Found, for the K salt : Fe, 24·3. Calc. for K_2FeF_5 : Fe, 24·4. Found, for the Cs salt : Fe, 20·9. $CsFeF_4$ requires Fe, 20·9%].

Cobalt Trifluoride.—Cobaltous fluoride was fluorinated by elemental fluorine according to Ruff and Ascher (*Z. anorg. Chem.*, 1929, **183**, 193), to a mixture shown by iodometric determination to contain 88% of CoF_3. Fluorine was determined by decomposition with sodium carbonate solution and precipitation as calcium fluoride (Found : F, 47·8. Calc. for 88% CoF_3 + 12% CoF_2 : F, 47·4%). We thank Dr. E. G. Walaschewski for this preparation. The susceptibility was corrected for the presence of 12% of CoF_2.

Cupric Fluoride Dihydrate.—The commercial product was recrystallised from dilute hydrofluoric acid, and the copper content determined iodometrically (Found : Cu, 46·4. Calc. for $CuF_2,2H_2O$: Cu, 46·2%).

Compounds of Platinum Metals.—Rhodium tetrafluoride (Found: Rh, 53·8; Br, 3·0. Calc. for RhF_4: Rh, 57·4; Br, 0%), palladium trifluoride (Found: Pd, 64·3. Calc. for PdF_3: Pd, 65·2%), platinum tetrafluoride (Found: Pt, 74·0. Calc. for PtF_4: Pt, 72·0%), sodium heptafluororhodate(IV) (Found: Rh, 33·2. Calc. for Na_3RhF_7: Rh, 33·7%), and potassium hexafluoroplatinate (Found: Pt, 19·9. Calc. for K_2PtF_6: Pt, 20·1%) were prepared and analysed as described previously (Sharpe, *J.*, 1950, 3444). Qualitative analysis showed the freedom of the compounds from contamination by iron, cobalt, or nickel.

Auric Fluoride and Silver Tetrafluoroaurate.—These were obtained and analysed according to Sharpe (*J.*, 1949, 2901) (Found: Au, 78·7. Calc. for AuF_3: Au, 78·4%) (Found: Au, 51·3. Calc. for $AgAuF_4$: Au, 51·7%).

Magnetic Measurements.—The Gouy method was used. For details see Part III (*J.*, 1950, 851).

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683. Solanum *Alkaloids. Part VIII.** *Solamargine, a New Alkaloid from* Solanum marginatum.

By LINDSAY H. BRIGGS, E. G. BROOKER, W. E. HARVEY, and A. L. ODELL.

From the green fruit of *S. marginatum* a new alkaloid, solamargine, $C_{45}H_{73}O_{15}N$, has been isolated. On hydrolysis with aqueous-alcoholic hydrochloric acid, conditions where there is complete solution throughout, it affords, solasodine, glucose, and rhamnose. With 2—3% aqueous hydrochloric acid partial hydrolysis occurs with liberation of rhamnose and formation of solasodine glucoside as an insoluble hydrochloride, producing solasodine and glucose on further hydrolysis. The molecular formula corresponds with the union of solasodine with one molecule of glucose and two of rhamnose, so that the partial structure, rhamnose–rhamnose–glucose–solasodine, is indicated for solmargine.

Solanum marginatum, a shrub endemic to the Nile delta, Abyssinia, and Italy, has been introduced into New Zealand where it now grows wild round Auckland, Wellington, and in the Marlborough Sounds of the South Island. The green fruits are large, up to 5 cm. in diameter, and extremely bitter.

From the green fruit a new glycosidic alkaloid, $C_{45}H_{73}O_{15}N$, has been islated and characterised as its picrate and picrolonate; the name solamargine is proposed for it. It forms a crystalline benzoate, which is unsuitable for characterisation since the benzoic acid sublimes when the salt is heated.

Hydrolysis of solamargine with aqueous-alcoholic hydrochloric acid at 100°, conditions where there is complete solution throughout, afforded, on cooling, a crystalline hydrochloride, which on basification yielded solasodine, identified by mixed melting points of the free base and its picrate. The remaining solution, after deionisation, was examined for sugars by several variations of paper chromatography: only glucose and rhamnose were detected. When 2—3% aqueous hydrochloric acid, which hydrolyses solanine, solasonine, and solauricine completely, was used, a crystalline hydrochloride separated. The free base, m. p. 251—253° (decomp.), obtained from it, could only be crystallised from a mixture of methyl alcohol and concentrated ammonia and was shown to be solasodine β-glucoside, $C_{33}H_{53}O_7N$. After removal of ionic material from the solution arising from this hydrolysis, crystalline rhamnose was obtained and identified by its mixed melting point and its osazone.

Hydrolysis of solasodine glucoside with aqueous-alcoholic hydrochloric acid afforded

* Part VII, *J.*, 1952, 1654.

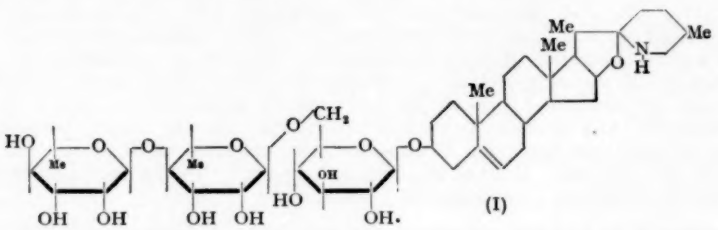
solasodine hydrochloride and from the resulting deionised sugar solution only one spot could be obtained by paper chromatography. This corresponded to glucose from a control solution, and was confirmed by the preparation of glucosazone. Solasodine glucoside also affords solasodine when sublimed in a high vacuum.

Solasodine glucoside has a more negative rotation ($[\alpha]_D$ $-122° \pm 4°$) than solasodine ($[\alpha]_D$ $-113{\cdot}5° \pm 2°$). Since α-glucopyranosides tend to have a positive rotation and the corresponding β-glucopyranosides a negative rotation it appears that glucose is joined to solasodine by a β-linkage. Solasodine glucoside, however, resisted hydrolysis for six months when dissolved with a preparation of emulsin in a sodium acetate–acetic acid buffer solution of pH 4·6, capable of immediately hydrolysing amygdalin. Glucose was however readily detected thereafter by paper chromatography on hydrolysis with aqueous-alcoholic hydrochloric acid.

An attempt was made to prepare solasodine β-glucoside by condensation of solasodine with acetobromoglucose in the presence of silver oxide under anhydrous conditions. It gave, however, solasodine hydrobromide.

The molecular formula of solamargine agrees with the union of solasodine with a hexose and two methyl pentose units. Since glucose and rhamnose were the only sugars formed on hydrolysis the above evidence indicates that solamargine is constituted as rhamnose–rhamnose–glucose–solasodine.

Solamargine does not reduce Fehling's and Tollens's reagents, showing that the sugars are joined through their potential aldehyde groups. The glucose linkage has already been shown to be β and from the great ease of hydrolysis of the rhamnose units it is probable that this sugar also is joined through β-linkages. The above evidence, together with further results on the position of the linkages in the sugar moiety to be submitted later, suggests that solamargine is probably (I).



(I)

That solasodine β-glucoside was a derivative of solasodine was early shown by colour reactions given with *p*-substituted aldehydes and resorcinol (Part II, *J.*, 1942, 3). Dehydrogenation with selenium yielded 2-ethyl-5-methylpyridine, identified as its picrate and styphnate. The significance of this for the structure of solasodine was referred to in Part V (*J.*, 1950, 3013). Solasodine glucoside, in contrast with the free base, readily forms easily crystallisable salts with inorganic and organic acids. With nitrous acid it forms a *N*-nitroso-derivative, but some hydrolysis occurs at the same time since *N*-nitrososolasodine (Part V, *J.*, 1950, 3013) was recovered from the mother-liquors.

Part of the solamargine is completely hydrolysed when treated with 2—3% aqueous hydrochloric acid since, besides solasodine glucoside and rhamnose, solasodine can also be isolated after chromatography of the basic fraction and glucose can be identified as glucosazone in the sugar fraction.

Experimental

M. p.s marked * were taken in evacuated tubes. The analyses are by Drs. Weiler and Strauss, Oxford, Mr. J. Mills, Adelaide University, or Dr. T. S. Ma and Mr. A. D. Campbell, University of Otago, Dunedin.

Green berries of *S. marginatum*, collected in June at Mt. Wellington near Auckland, were passed through a juice extractor, and the resulting juice was filtered through calico bags, boiled for a few minutes, and stored in sterile bottles under toluene. The berries were worked up in small batches to avoid undue exposure to the air since this results in darkening of

the juice and makes the isolation of the pure alkaloid much more difficult. The residual pulp was extracted three times by storage in aqueous acetic acid (3%), and the extracts were treated in the same manner as the juice. After settling, the black supernatant liquor was carefully siphoned off, boiled, and filtered through steam-jacketed, gravity filters. From the filtered solution crude solamargine was precipitated by slow passage of ammonia which was continued until the mixture was cool. The glycoside was taken up in boiling 3% acetic acid solution, then reprecipitated by ammonia, and the whole process repeated. The crude glycoside was then extracted (Soxhlet) to free it from inorganic material, shown to be magnesium ammonium phosphate which behaves like an alkaloid in being soluble in acids and insoluble in ammoniacal solutions. Final purification was brought about by repeated crystallisation from 50% alcohol, with charcoal at first, the yield being 0·3—0·5%. A sample, crystallised ten times, formed thin, colourless, pointed plates, m. p. 301° (decomp.) * after sintering at 270°, $[\alpha]_D^{20}$ −105° ±4° (*l*, 0·25; *c*, 0·986 in methyl alcohol) (Found: C, 62·3; H, 8·45; N, 1·7. $C_{45}H_{73}O_{15}N$ requires C, 62·3; H, 8·5; N, 1·6%). *Solamargine* is very soluble in methyl and ethyl alcohol, and from aqueous-alcoholic solutions containing more than 50% alcohol it separates in gelatinous form.

Solamargine picrate, formed from its components in boiling 50% alcohol, after repeated crystallisation from 20% alcohol containing a trace of picric acid, yielded yellow needles, m. p. 188—189° (decomp.)* (Found: C, 55·6; H, 7·2. $C_{45}H_{73}O_{15}N,C_6H_3O_7N_3$ requires C, 55·8; H, 6·9%). That no change had occurred in the formation of this derivative was shown by its reconversion into solamargine, m. p. and mixed m. p. 301° (decomp.)*, by lithium hydroxide solution at 100°.

Solamargine picrolonate was formed overnight from the components in hot 50% alcohol. After four crystallisations from 80% alcohol it yielded long, yellow needles, m. p. 204—205° (decomp.) (Found: C, 57·7; H, 7·1; N, 6·7. $C_{45}H_{73}O_{15}N,C_{10}H_8O_5N_4$ requires C, 58·3; H, 7·2; N, 6·2%).

Solmargine benzoate separated overnight in needles from a hot solution of the components in 60% alcohol. No definite m. p. was observed but long pointed plates sublimed with m. p. 119—120° (benzoic acid has m. p. 121°). The loss on heating overnight at 100°/20 mm. was 11·4% ($C_{45}H_{73}O_{15}N,C_7H_6O_2$ requires $C_7H_6O_2$, 12·3%).

Complete Hydrolysis of Solamargine.—Solamargine (250 mg.) was heated at 100° for ½ hour in 10% hydrochloric acid (10 c.c.). Sufficient alcohol (12 c.c.) to effect complete solution was then added and the heating continued for 1½ hours. Needles formed on cooling (yield 93 mg.), with m. p. 307·5—308° (decomp.)* after recrystallisation from 80% alcohol. The free base was recovered from this hydrochloride by treatment of a suspension with excess of ammonia at 100° for 1 hour. Repeated crystallisation from 80% alcohol, methyl alcohol, and acetone, successively, afforded colourless, hexagonal plates, m. p. and mixed m. p. with authentic solasodine, 199·5—200°.* The picrate crystallised from 80% alcohol in rods, m. p. and mixed m. p. with solasodine picrate, 142—143° (decomp.).

Identification of the Sugars Obtained on Complete Hydrolysis of Solamargine.—In a further experiment where hydrolysis was complete, the solasodine hydrochloride was filtered off and the filtrate heated for a further half hour at 100° to remove alcohol. After removal of a second crop of solasodine hydrochloride the residue was neutralised with silver carbonate, the silver residues were filtered off and washed with water, and the combined filtrates saturated with hydrogen sulphide. After filtration, hydrogen sulphide was removed by aeration and the sugar solution concentrated in a vacuum at 45—50°. Aliquots of this solution were examined for sugars by paper chromatography at 18°, on Whatman No. 1 filter paper strips, 10 × 48 cm. The unknown mixture of sugars was chromatographed according to the general procedure of Jermyn and Isherwood (*Biochem. J.*, 1949, **44**, 402) with various solvents, and a control spot of solution containing known sugars was placed alongside or superimposed on an unknown spot placed alongside a second unknown spot.

(*a*) Development of the unknown sugar spot with the water-poor phase of the system ethyl acetate–acetic acid–water (3 : 1 : 3), freshly prepared, for 30 hours followed by spraying with ammoniacal silver nitrate solution (Partridge, *Nature*, 1946, **158**, 270) afforded two spots corresponding to glucose and rhamnose from control solutions.

(*b*) Development of the unknown sugar spot with the water-poor phase of the solvent system ethyl acetate–pyridine–water (2 : 1 : 2), and spraying with ammoniacal silver nitrate solution also afforded two spots corresponding to glucose and rhamnose from control solutions.

(*c*) The solvent system *n*-butanol–pyridine–water (3 : 1 : 1) (Hough, Jones, and Wadman, *J.*, 1950, 1702) was used as developing solvent, and aniline hydrogen phthalate as spraying reagent (Partridge, *Nature*, 1949, **164**, 443).

In all cases only two spots were obtained, corresponding to glucose and rhamnose.

Partial Hydrolysis of Solamargine to Solasodine β-Glucoside.—Solamargine (10 g.), dissolved in 2% aqueous hydrochloric acid (100 c.c.), was heated at 100° for 1 hour. A precipitate formed in a few minutes and was voluminous and gelatinous after 15 minutes. After some time, the hydrochloride was filtered off, suspended in water, and heated with excess of ammonia for 1 hour. The product could not be crystallised from any of twenty common solvents but crystallised from methyl alcohol–ammonia (*d* 0·880) and, after repeated crystallisation, formed long, colourless needles, m. p. 251—253° (decomp),* $[\alpha]_D^{20}$ −122°±4° (*l*, 0·25; *c*, 0·954 in methyl alcohol) (Found: C, 69·3, 69·2; H, 9·4, 9·5; N, 2·8. $C_{33}H_{53}O_7N$ requires C, 68·8; H, 9·3; N, 2·4%). In a determination of active hydrogen atoms (Zerewitinoff) a solution of methylmagnesium iodide in anisole gave an evolution of methane from cholesterol in good agreement with the theoretical value but with *solasodine β-glucoside* the reagents gelatinised on mixing and no gas was evolved after several hours at 25°.

It was not possible to obtain a crystalline sugar when the filtrate from the above hydrochloride was treated with silver carbonate and worked up in the usual way. This was achieved, however, in the following manner. Solamargine (20 g.) was hydrolysed by water (200 c.c.) and concentrated sulphuric acid (2 c.c.) at 100° for 2 hours. The final clear solution was decolourised with charcoal, treated with excess of barium carbonate at 100° for 1 hour, and filtered. The free base was recovered from the residue by extraction with methyl alcohol. The filtrate was concentrated at 100° to a syrup and placed in a vacuum-desiccator. When rubbed, the product solidified and, on trituration with absolute alcohol, small prisms were formed, m. p. and mixed m. p. with rhamnose, 91—93°. An osazone prepared from this material crystallised from 80% alcohol in yellow needles, m. p. and mixed m. p. with rhamnose phenylosazone, 184·5—185°.

In a preliminary test for rhamnose in the above experiment by Dehn, Jackson, and Ballard's ammonium molybdate method (*Ind. Eng. Chem., Anal.*, 1932, **4**, 413) we found that the concentration of the rhamnose solution affects the colour produced. When the reagent is added to a few mg. of rhamnose the solution changes from yellowish to green as recorded, but in more dilute solution, comparable with the above hydrolysis solution, a bluish-green colour forms, becoming green overnight. The hydrolysis solution behaved similarly.

In additional hydrolyses of solamargine under approximately the same experimental conditions as above, the basic reaction product was chromatographed on alumina from chloroform solution. The material obtained from the first fraction of the eluate, after repeated crystallisation from methanol and acetone, separated in hexagonal plates, m. p. and mixed m. p. with solasodine, 196—198°. The soluble portion from the hydrolysis yielded glucosazone, m. p. and mixed m. p. 205·5—206° (decomp.).

Salts of solasodine β-glucoside crystallised from alcohol to which a little water was added for clarification but only a few were isolated. The *picrate* formed needles, m. p. 191° (Found: C, 58·4, 58·1; H, 7·0, 6·9; N, 7·4. $C_{33}H_{53}O_7N,C_6H_3O_7N_3$ requires C, 58·2; H, 7·0; N, 7·0%). The tartrate (needles), citrate (needles), and oxalate (plates) had m. p. 216°, 165°, 308°, respectively, all with decomposition. Formation of a hydrochloride (see above), hydrobromide, hydriodide, sulphate, nitrate, chloroplatinate, chloroaurate (all needles) and benzoate (plates) was also observed.

To solasodine β-glucoside (2 g.) in alcohol (15 c.c.) and glacial acetic acid (1 c.c.) a solution of sodium nitrite (600 mg. in 3 c.c.) was added. The crystalline *nitroso*-derivative, which formed overnight, recrystallised from 80% alcohol as needles, m. p. 233·5—234° (decomp.) (Found: C, 65·5, 65·8, 66·0; H, 9·0, 8·6, 9·0; N, 5·9, 5·2, 5·4. $C_{33}H_{52}O_6N_2$ requires C, 65·5; H, 8·7; N, 4·6%). A fraction of the main product was not readily soluble in 80% alcohol and after repeated crystallisation from alcohol formed rectangular prisms, m. p. and mixed m. p. with *N*-nitrososolasodine, 260—261° (decomp.) (Found: C, 73·0; H, 9·3; N, 6·6, 6·55. Calc. for $C_{27}H_{42}O_3N_2$: C, 73·3; H, 9·6; N, 6·3%). *N*-Nitrososolasodine β-glucoside is unchanged by aqueous or alcoholic ammonia at 100° (1 hour).

Hydrolysis of Solasodine β-Glucoside and Identification of Glucose.—(a) *By paper chromatography.* Solasodine β-glucoside (5 mg.) was hydrolysed by a hot mixture of 10% hydrochloric acid (0·25 c.c.) and alcohol (1 c.c.). After removal of the solasodine hydrochloride (needles) the filtrate was treated with silver carbonate, and the sugar solution worked up as previously described. Development of a spot of the resultant solution with the water-poor phase of the system ethyl acetate–acetic acid–water (3 : 1 : 3) as developing solvent and ammoniacal silver nitrate as spraying reagent afforded only one spot, corresponding to glucose from control experiments.

(b) *By formation of glucosazone.* Solasodine β-glucoside (100 mg.) was hydrolysed as above and the sugar solution, worked up as before, concentrated in a vacuum over sulphuric acid at room temperature to *ca.* 2 c.c. Treatment with phenylhydrazine in the usual way followed by recrystallisation of the product from acetone afforded yellow needles, m. p. and mixed m. p. with glucosazone, 205—206° (decomp.).

Sublimation of Solasodine β-Glucoside.—When heated at *ca.* 190—200° in a high vacuum solasodine β-glucoside decomposed and solasodine sublimed. The product separated from alcohol as hexagonal plates, m. p. and mixed m. p. with solasodine 201—202·5°.

Dehydrogenation of Solasodine β-Glucoside.—Solasodine β-glucoside (5 g.) and selenium (15 g.), intimately mixed, were heated under nitrogen at 280°. A greenish liquid distilled, and at 290—300° severe frothing occurred. Heating was continued for 4 hours at 320°. The dark distillate was acidified with hydrochloric acid and extracted with ether. The aqueous fraction was made alkaline with solid sodium hydroxide and then yielded to ether a small amount of dark oil. On distillation in a micro-column (Craig, *Ind. Eng. Chem., Anal.*, 1936, **8**, 219) three fractions were collected: (*a*) b. p. up to 100° (23·5 mg.), slightly yellow; (*b*) b. p. 100—150° (24·0 mg.), pale brown; and (*c*) b. p. 150—200° (31·5 mg.), brown, partly solid. Fractions (*a*) and (*b*) gave identical picrates when treated with a saturated solution of picric acid in alcohol and, after repeated crystallisation from alcohol, had m. p. 141·5—142·5°, undepressed by authentic 2-ethyl-5-methylpyridine picrate, kindly presented by Dr. Lyman C. Craig (Found: C, 48·2; H, 3·9; N, 16·0. Calc. for $C_8H_{11}N,C_6H_3O_7N_3$: C, 48·0; H, 4·0; N, 16·0%). The mother-liquors from the picrate were decomposed with lithium hydroxide solution (cf. Burger, *J. Amer. Chem. Soc.*, 1945, **67**, 1615) and then yielded to ether an oil which was converted into the styphnate in methyl alcoholic solution. The yellow needles formed on cooling had m. p. 169·5°. Prelog and Szpilfogel (*Helv. Chim. Acta*, 1942, **25**, 1306) record m. p. 170° for the styphnate of 2-ethyl-5-methylpyridine.

We are greatly indebted to Messrs. N. E. Webb and P. H. Hocquard for supplies of the fruit from Marlborough Sounds, one of us (W. E. H.) for a Shirtcliffe Graduate Bursary, and one of us (E. G. B.) for a University Research Fund Fellowship. Assistance is also gratefully acknowledged from the Chemical Society, The Australian and New Zealand Association for the Advancement of Science, the Royal Society of New Zealand, and the Research Grants Committee of the University of New Zealand for continued grants.

Auckland University College, Auckland, New Zealand. [*Received, May 7th*, 1952.]

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684. Solanum *Alkaloids. Part IX.* The Relation between Constitution and Basicity in Solasodine, its Derivatives, and Solanidine.*

By H. Bloom and Lindsay H. Briggs.

A relation exists between the constitution of bases in this series and their basicity, depending on the presence or absence of the oxide ring.

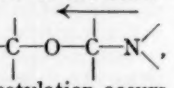
Utilising Ingold's micro-procedure (*Helv. Chim. Acta*, 1946, **29**, 1929) for estimation of the dissociation constants of bases, already employed in constitutional studies of polymethyleneimines (Prelog *et al.*, *ibid.*, 1948, **31**, 1325; 1949, **32**, 544) and strychnine bases (Prelog and Häfliger, *ibid.*, 1949, **32**, 1851) we have measured the basicity of the following compounds in terms of their pK_b values. The results are recorded in the following Table.

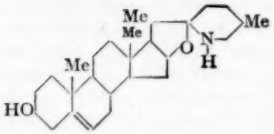
	Compound	pK_b		Compound	pK_b
I	Solasodine	6·30, 6·32	VII	Dihydrosolasodenol	4·36
II	Solasonine	6·26	VIII	Dihydrosolasodanol	4·28
III	Solmargine	6·25, 6·36	IX	Dihydrosolaso-3 : 5-diene [2]	4·16
IV	Solasodamine [1]	6·18, 6·23, 6·32	X	Dihydro-*N*-methylsolasodenol [2]	5·50, 5·66
V	Solasodanol	6·36	XI	Solanidine	5·38
VI	Solaso-3 : 5-diene	6·20			

[1] A new tetrasaccharide derivative of solasodine isolated from *S. sodomaeum*, *S. auriculatum*, and *S. marginatum*, constituted as rhamnose–rhamnose–galactose–glucose–solasodine, with probable sugar linkages, 1 : 1,4 : 1,4 : 1,6, respectively (forthcoming publications).

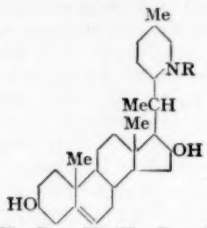
[2] New compounds to be described in detail later.

* Part VIII, preceding paper.

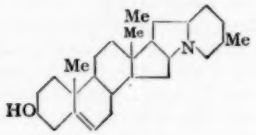
Solasodine (I) and all its derivatives with the oxygen bridge intact, *viz.*, (II), (III), (IV), (V), and (VI), are relatively weak bases with an approximate pK_b value of 6·2—6·3. This weak basicity is obviously due to the inductive effect of the ether-oxygen atom attached to the same carbon atom as the nitrogen atom, *i.e.*,  , an effect weaker than that occurring in amides, and it explains why *O*-acetylation occurs in solasodine in preference to *N*-acetylation and why *O*-benzoyl derivatives may be obtained and not *N*-benzoyl derivatives (cf. Part VII, *J.*, 1952, 1654).



(I)



(VII; R = H) (X; R = Me)



(XI)

When the oxide ring is broken, however, as in dihydrosolasodenol (VII) and its derivatives, *viz.*, (VIII) and (IX), no such inductive effect occurs and these bases are much stronger, with a pK_b value of 4·2—4·3. In contrast with the first series of compounds no difference can be detected in the ease of acetylation or benzoylation of the secondary hydroxyl and amino-groups (cf. Part VII, *loc. cit.*).

When dihydrosolasodenol is converted into the tertiary base, dihydro-*N*-methylsolasodenol (X), the basicity decreases and the pK_b value (5·5) is comparable with that of the tertiary base, solanidine (XI).

Experimental

Solutions of 50—100 mg. of the compounds in 60% alcohol–water (carbon dioxide-free) were titrated at 19·5—20·5° with 0·1N-hydrochloric acid by use of a semimicro-burette. pH readings were carried out with a Cambridge pH meter with an accuracy of ±0·02 pH unit. The pH at half-neutralization was estimated from the plot of pH against the volume of hydrochloric acid added, within ±0·05 unit.

We are greatly indebted to Professor Prelog, Zürich, for a supply of solanine and to Messrs. R. N. Seelye and E. G. Brooker for the preparation and purification of some of the compounds. Assistance is also gratefully acknowledged from the Chemical Society, and the Royal Society of New Zealand, for continued grants.

Auckland University College, Auckland, New Zealand. [*Received, May 7th*, 1952.]

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685. *The Reaction between Indole and Acetic Anhydride.*

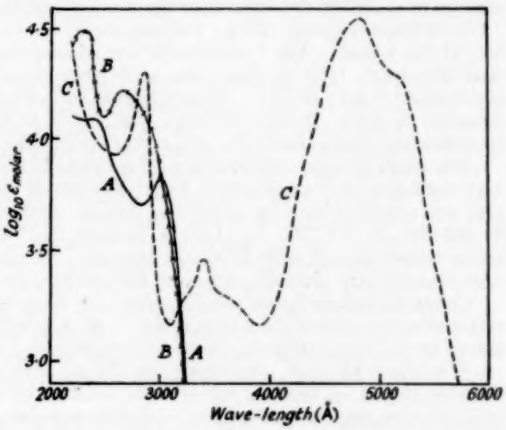
By J. E. Saxton.

The action of acetic anhydride and acetic acid on indole at the boiling point of the mixture affords 1 : 3-diacetylindole and a by-product, not previously observed, considered to be 1 : 1-di-(1-acetyl-3-indolyl)ethylene.

In connection with synthetical studies in the strychnine series, considerable quantities of 3-acetylindole were required. The principal methods which have been used for the preparation of this compound are the reaction of indole with acetic anhydride at 180—200° (Baeyer, *Ber.*, 1879, **12**, 1314; Ciamician and Zatti, *Ber.*, 1889, **22**, 1977; Zatti and Ferratini, *Ber.*, 1890, **23**, 1360) and of indolylmagnesium halides with acetyl chloride (Oddo and Sessa, *Gazzetta*, 1911, **41**, I, 234; Majima, *Ber.*, 1922, **55**, 3871; Baker, *J.*, 1946, 462).

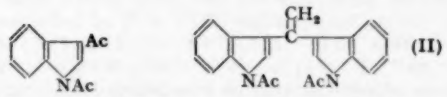
They give varying yields of a mixture of mono- and di-acetylindoles. For example, while Majima claims a 93% yield of 3-acetylindole, Oddo and Sessa, and also Baker, make no such claims, and repetition of their experiments shows that the yield is very unsatisfactory.

For this reason, the reaction of indole with acetic anhydride was preferred as a preparative method, but it cannot easily be adapted to a large-scale preparation owing to the conditions used (180—200° in sealed tubes). In addition the dark product had to be crystallised several times in order to obtain pure diacetylindole (I). Accordingly, the reaction was carried out at 147° for periods of 24—48 hours. Pure acetic anhydride gave an oil, which on crystallisation gave a low yield of diacetylindole, but the addition of 10% of acetic acid to the reaction mixture gave after 24 hours a product which crystallised readily during the removal of the solvent *in vacuo* and on further crystallisation gave 55—60% yields of clean diacetylindole. The *N*-acetyl group of this compound was removed quantitatively at the room temperature by aqueous-alcoholic sodium hydroxide.

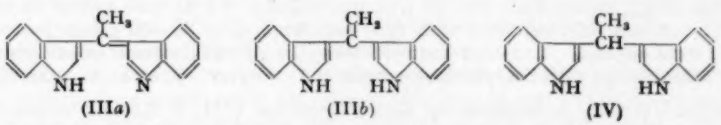


A, 1 : 1-*Di*-(1-*acetyl*-3-*indolyl*)*ethylene* (II) *in methanol.*
B, 1-3′-*Indolyl*-1-3″-*indolylidene-ethane* (III) *in methanol.*
C, 1-3′-*Indolyl*-1-3″-*indolylidene-ethane in methanolic* HCl.

The crude diacetylindole was contaminated by 5—10% of a by-product, $C_{22}H_{18}O_2N_2$, for which structure (II) is proposed. The *N*-acyl groups are readily removed, to give a



compound $C_{18}H_{14}N_2$, which must be (III*a* or *b*). This substance is a very weak base, which gives rise to deeply coloured salts of a type previously reported by Borsche and Groth (*Annalen*, 1941, **549**, 238). It is very readily reduced to a dihydro-derivative, $C_{18}H_{16}N_2$, m. p. 162°, which has all the characteristics of a β-substituted indole and must be (IV). The preparation of this (IV) from indolylmagnesium bromide and acetaldehyde has previously been reported by Oddo and Toffoli (*Gazzetta*, 1934, **64**, 359) who gave m. p. *ca.* 160° (not sharp). An independent synthesis of this compound from indole, paraldehyde, and zinc chloride has confirmed the structure (IV) for the reduction product, and hence (II) for the original by-product.



The structure of the de-acetylated product has not been determined, but the available evidence supports (III*a*) rather than (III*b*). Thus, the presence of formaldehyde among

the ozonolysis products of (III) could not be demonstrated. Further, in the infra-red region the substance does not exhibit the absorption bands characteristic of a methylene group, and in this respect resembles (IV). In contrast, the spectrum of (II) has pronounced maxima at 9·98, 10·68, and 11·15 μ, showing unequivocally the presence of a methylene group.

The absorption of (III) in the ultra-violet region is shown in the Figure, and a noteworthy feature is the striking change that occurs on salt formation.

Experimental

Reaction between Indole and Acetic Anhydride.—Indole (25 g.), acetic acid (25 c.c.), and acetic anhydride (225 c.c.) were refluxed for 24 hours. The solvent was removed *in vacuo*, and the residue, which was crystalline at 100°, recrystallised from ethanol. 1 : 3-Diacetylindole (16—18 g.; pure material from 24—26 g. of crude material) was obtained as colourless needles, m. p. 150—151° (Found: N, 7·0. Calc for $C_{12}H_{11}O_2N$: N, 7·0%). Zatti (*Ber.*, 1889, **22**, 1978) reports m. p. 151°; the substance also crystallised from benzene.

1 : 3-Diacetylindole (20 g.) was suspended in ethanol (100 c.c.), and sodium hydroxide (50 c.c. of 2N) added. The mixture was stirred and warmed if necessary until the diacetylindole had dissolved. The product was then precipitated by dilution with water, collected, and crystallised from ethanol. 3-Acetylindole was obtained as long, colourless prisms, m. p. 191° (Found: C, 75·9; H, 5·8; N, 8·8. Calc. for $C_{10}H_9ON$: C, 75·5; H, 5·7; N, 8·8%), in almost quantitative yield; Zatti (*loc. cit.*) reports m. p. 190—191°.

The small amount of insoluble residue after the first crystallisation of the crude diacetylindole was collected and crystallised from acetone or dioxan. 1 : 1-*Di*-(1-*acetyl*-3-*indolyl*)*ethylene* (II) was obtained as long, colourless rods or needles, m. p. 220—221° (Found: C, 77·1, 77·1; H, 5·3, 5·5; N, 8·1, 7·9. $C_{22}H_{18}O_2N_2$ requires C, 77·2; H, 5·3; N, 8·2%). This gave an orange colour when heated with Ehrlich's reagent; its deep red solution in concentrated sulphuric acid became dark greenish-brown on the addition of potassium dichromate.

Complete separation of the diacetylindole from the by-product by fractional crystallisation resulted in substantial losses of material. In order to ensure the optimum yield of 3-acetylindole, the by-product was removed in the hydrolysis stage, by the following procedure:

A mixture of crude diacetylindole (30 g.) with ethanol (225 c.c.) and sodium hydroxide solution (75 c.c. of 2N) was stirred until solution of the diacetylindole was complete. The by-product remained as an insoluble crystalline powder (3 g.) and was collected and washed with a little warm ethanol. 3-Acetylindole was precipitated from the combined filtrates on dilution with water. It separated from ethanol as long, colourless prisms, m. p. 191° (18 g.).

Crystallisation of 1 : 1-di-(1-acetyl-3-indolyl)ethylene from aqueous pyridine, or treatment with hot aqueous-alcoholic alkali, followed by crystallisation from dioxan, gave 1-3′-*indolyl*-1-3″-*indolylidene-ethane* (or its tautomeride) (III*a* or *b*) as colourless rhombs, m. p. 232—234° (decomp.) (Found: C, 83·5, 83·9; H, 5·3, 5·4; N, 11·2, 11·3; *C*-Me, 5·7%; *M*, 234, 273. $C_{18}H_{14}N_2$ requires C, 83·7; H, 5·4; N, 10·9; *C*-Me, 5·8%; *M*, 258). In hot dilute hydrochloric acid this gave an orange-red solution from which long, orange-red needles of the *hydrochloride* separated on cooling. After drying at 100° for 8 hours, it was obtained as greenish-black plates with a metallic lustre, decomp. > 155° (Found: C, 73·0; H, 5·5. $C_{18}H_{14}N_2$,HCl requires C, 73·4; H, 5·1%).

1 : 1-*Di*-3′-*indolylethane* (IV).—(*a*) 1-3′-Indolyl-1-3″-indolylidene-ethane (1·0 g.) was hydrogenated in dioxan–ethanol at room temperature and pressure with a palladised strontium carbonate catalyst. 1 Mol. of hydrogen was rapidly absorbed and hydrogenation then ceased. The filtered solution was evaporated *in vacuo*, and the residue crystallised from ethanol. 1 : 1-*Di*-3′-*indolylethane* (0·8 g.) was obtained as colourless prisms, m. p. 162° (Found: C, 83·5; H, 6·2; N, 10·7. $C_{18}H_{16}N_2$ requires C, 83·1; H, 6·2; N, 10·8%). This substance gave a magenta colour with Ehrlich's reagent which gradually became blue.

(*b*) Indole (2 g.), paraldehyde (0·4 g.), and zinc chloride (0·5 g.) were heated on the steam-bath for 5 hours and then extracted with light petroleum (b. p. 40—60°), and the residue was crystallised from ethanol. 1 : 1-Di-3′-indolylethane (0·5 g.) was obtained as colourless prisms, m. p. and mixed m. p. with the previous sample 162° (Found: C, 83·4; H, 6·3; N, 10·8%).

The author is grateful to Professor Sir Robert Robinson, O.M., F.R.S., for his interest in the work.

The Dyson Perrins Laboratory, Oxford. [*Received, May 10th*, 1952.]

686. *Glow-discharge Electrolysis. Part I. The Anodic Formation of Hydrogen Peroxide in Inert Electrolytes.*

By R. A. Davies and A. Hickling.

The electrolysis of dilute solutions of inert electrolytes has been investigated, with an anode withdrawn from the solution, by passing an electrical discharge at reduced pressure to the liquid surface. The main anodic product initially formed is hydrogen peroxide in amount proportional to the quantity of electricity passed; as this accumulates in the solution a decomposition reaction sets in and ultimately a stationary concentration of hydrogen peroxide is attained. The amount of hydrogen peroxide present in the solution after the passage of a given quantity of electricity is substantially independent of the current used and of factors affecting the nature of the discharge, and it can be accurately expressed by an equation of the form

$$(H_2O_2)\ \text{equivs.} = V(1 - e^{-\frac{akq}{V}})/k$$

where q is the quantity of electricity in faradays, V is the volume of the solution, k is a velocity coefficient for the decomposition reaction, and a is a factor (value 1·1—1·9) expressing the number of equivalents of hydrogen peroxide initially formed for each faraday of electricity passed. The process is fundamentally the same for different solutions varying in pH from 1 to 9, with, however, some decrease in the amount of hydrogen peroxide formed at the extremes of this range; in strongly alkaline solutions no hydrogen peroxide can be detected, probably owing to its ready anodic decomposition by discharge of the perhydroxyl ion. The general features of the electrolysis are interpreted by the primary formation in solution of the hydroxyl radical, mainly by electrolytic action although the possibility of some direct dissociation of water molecules is not excluded; dimerisation then occurs to give hydrogen peroxide, which, when it attains a sufficient concentration, decomposes by interaction with hydroxyl radicals as fast as it is formed.

The mechanism of electrode reactions in conventional electrolysis is complicated by the fact that the reactions occur at the surface of the electrodes used for passage of current through the solution, and in many cases the electrode material undoubtedly exercises a specific influence. This can be avoided by withdrawing the electrode under investigation into the gas space above, and on then working at reduced pressure and applying a moderately high voltage substantial currents can be passed to the liquid surface in the form of a glow-discharge. The technique was developed long ago (Gubkin, *Ann. Physik*, 1887, **32**, 114; Klüpfel, *ibid.*, 1905, **16**, 574; Makowetsky, *Z. Elektrochem.*, 1911, **17**, 217) but has since been used only to a limited extent, mainly by Klemenc and his co-workers (*Z. Elektrochem.*, 1914, **20**, 485; 1931, **37**, 742; *Z. physikal. Chem.*, 1927, **130**, 378; 1931, **154**, 385; 1933, **166**, 343; 1935, **27**, *B*, 369; 1937, **179**, 1; 1938, **182**, 91; 1938, **40**, *B*, 252; 1938, **183**, 217, 297; *Z. anorg. Chem.*, 1939, **240**, 167; *Monatsh.*, 1944, **75**, 42; 1946, **76**, 38; 1948, **78**, 243; 1950, **81**, 122; see also Cousins, *Z. physikal. Chem.*, 1929, **4**, *B*, 440; Thon, *Compt. rend.*, 1933, **197**, 1114; Braunbek, *Z. Physik*, 1934, **91**, 184; Hickling, *J.*, 1934, 1772; Fichter and Kestenholz, *Helv. Chim. Acta*, 1940, **23**, 209; Pavlov, *Compt. rend. Acad. Sci. U.R.S.S.*, 1944, **43**, 236, 383, 385). In much of this work, however, rather complex conditions have been employed, with concentrated electrolyte solutions susceptible to oxidation and reduction, and no very definite conclusions have emerged; frequently it is difficult to discriminate between reactions brought about electrolytically and those initiated by the electrical discharge.

The present investigation was undertaken to ascertain the nature of the anodic process in the glow-discharge electrolysis of very dilute solutions of inert electrolytes in which the only likely electrolytic reaction was the discharge of the hydroxyl ion; earlier work suggested that hydrogen peroxide was the product arising in these circumstances and an extensive study has therefore been made of its formation and decomposition.

Experimental

The type of cell most frequently employed is shown in Fig. 1. It consisted of a boiling-tube, of approx. 5 cm. diameter, fitted with a rubber stopper carrying the cell components. The anode was usually a straight platinum wire which was carried in an adjustable holder so that it could be fixed at any distance from the electrolyte surface; the cathode was a spiral of platinum wire of 1 sq. cm. area contained in a glass tube of 1 cm. diameter closed at its lower end by a tight filter-paper plug which effectively prevented mixing of anolyte and catholyte. The anode and cathode compartments were each connected to a vacuum line of a conventional type which included a float manostat so that the pressure in the apparatus could be maintained constant over long periods.

The power supply was a Leland power unit providing voltages of 0—1500 v adjustable by means of a Variac transformer, and capable of a maximum output of 0·4 amp. at 1000 v. It was connected to the cell through a calibrated Sangamo Weston multirange ammeter and a ballast resistance of 2000 ohms. The discharge was started by momentarily including in the circuit the secondary of a spark coil. Once initiated the discharge was remarkably steady and took the form of a sharply defined cone between the tip of the anode (which became red hot) and the

Fig. 1. *Electrolytic cell.*

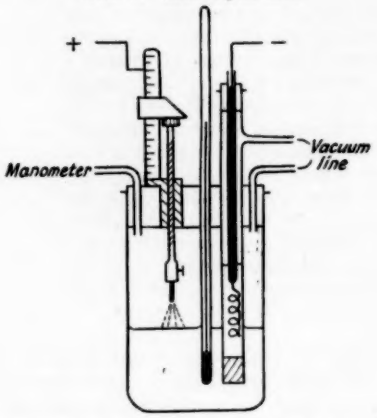
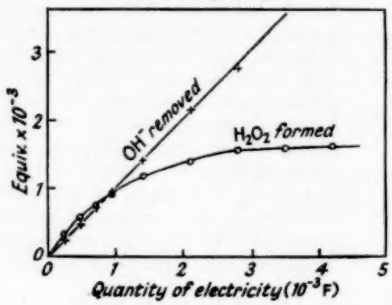


Fig. 2. *Glow-discharge electrolysis of* 0·05M-Na_2HPO_4.



electrolyte surface; the glow-spot in the surface was pink, and of area usually somewhat less than 1 sq. cm. The current passing would remain constant without adjustment over long periods, and the cell voltage (which is nearly all developed across the discharge) was in the range 500—700 v, varying according to experimental conditions. With increase of current the area of the glow-spot increased, and it appeared likely that the effective current density at the surface was approximately constant. The heat dissipated in the discharge is very considerable and this makes the control of temperature of the electrolyte difficult. In the present work the cell was cooled in ice-water, and the bulk temperature was found to rise very rapidly on electrolysis to about 15° and then more slowly to about 25°, the average bulk temperature over the greater part of electrolysis being between 20° and 25°; the local temperature in the glow-spot is probably appreciably higher than this.

The anolyte most frequently used was 50 ml. of a boiled-out solution of 0·05M-disodium hydrogen phosphate; the catholyte was 5 ml. of 0·5M-disodium hydrogen phosphate. The pH of the anolyte was initially 9·5, dropping rapidly on electrolysis to 6·4 and remaining constant at this value. The volume of the anolyte was measured after electrolysis and the solution then analysed. The amount of acid developed or hydroxyl ion discharge was found by titration with 0·01N-sodium hydroxide to the thymolphthalein end-point; check experiments had shown that hydrogen- and hydroxyl-ion migration in the anolyte was negligible under the conditions employed. The hydrogen peroxide was determined by titration with 0·01N-potassium permanganate in acid solution; this analysis was checked iodometrically in a number of cases and satisfactory agreement found. Blank determinations were carried out on the anolyte in all analyses.

The experimental conditions usually employed were: Anolyte: 50 ml. of unstirred 0·05M-

disodium hydrogen phosphate exposing a surface of approx. 19 sq. cm. Anode: platinum wire, the tip of which was 0·5 cm. from the electrolyte surface. Pressure: 50 mm. of mercury. Current: 0·075 amp. These are referred to as the " standard conditions " and are to be taken to apply when the experimental variables are not otherwise specified. In a number of instances the anolyte was stirred during electrolysis. This was achieved by introducing into the cell a small bar-magnet in a glass envelope and rotating it at uniform speed by means of an external field; check experiments showed that the presence of the magnetic field did not influence the results appreciably.

Results

Influence of General Factors.—Quantity of electricity. In Fig. 2 are shown the results of a series of experiments in which 0·05M-disodium hydrogen phosphate was electrolysed under standard conditions for different times; the number of equivalents of acid produced or hydroxyl ions removed, and of hydrogen peroxide formed, are plotted against the quantity of electricity passed expressed in faradays.

It is seen that the hydroxyl-ion discharge is accurately in accordance with that expected from Faraday's laws, while the hydrogen peroxide formed is initially proportional to the quantity of electricity passed, although the yield is slightly greater than 1 equivalent per faraday, but it decreases with increasing quantity of electricity and the amount of hydrogen peroxide in solution eventually approaches a limiting value. The general inference to be drawn is that two processes are occurring—an initial formation of hydrogen peroxide in amount proportional to the quantity of electricity passed, and a decomposition reaction as the peroxide accumulates in the electrolyte, a stationary state being ultimately attained. It is apparent that in investigating the influence of experimental variables it is necessary to distinguish their effects on the initial formation reaction from those on the system when the stationary state has been achieved.

Current. In Table 1 are shown the yields of hydrogen peroxide obtained for increasing quantities of electricity at each of three currents (0·10, 0·075, and 0·05 amp.) severally.

Table 1. *Influence of current on hydrogen peroxide formation.*

Quantity of electricity (10^{-3}F)	H_2O_2 formed (10^{-3} equiv.)			Quantity of electricity (10^{-3}F)	H_2O_2 formed (10^{-3} equiv.)		
	0·10	0·075	0·05 amp.		0·10	0·075	0·05 amp.
0·223	0·314	0·316	0·312	2·10	1·36	1·38	1·34
0·466	0·558	0·555	0·552	2·80	1·60	1·54	1·51
0·933	0·929	0·915	0·931	3·50	1·60	1·58	1·55
1·40	1·21	1·19	1·16	4·20	1·64	1·60	1·57

With increasing current the voltage of the discharge rose somewhat (from 560 to 600 volts) and the power dissipated in it increased very markedly (from 28 to 60 watts), but in spite of this the yields of hydrogen peroxide were substantially independent of the current used. Since the times of electrolysis were very different at the different currents, this result suggests that both the formation and the decomposition of the peroxide are due to some primary species which is produced electrolytically.

Volume of electrolyte. Table 2 shows the results obtained on varying the volume of the anolyte from 25 to 100 ml. under otherwise standard conditions, different quantities of electricity being used; the small quantity of $0{\cdot}373 \times 10^{-3}$ faraday corresponds to the state in which the formation reaction predominates and the decomposition reaction has not become

Table 2. *Influence of volume of anolyte.*

Volume of anolyte (ml.)	Quantity of electricity (10^{-3}F)	H_2O_2 formed (10^{-3} equiv.)	Volume of anolyte (ml.)	Quantity of electricity (10^{-3}F)	H_2O_2 formed (10^{-3} equiv.)	H_2O_2 concn. (N)
100	0·373	0·442	100	5·60	3·16	0·0316
75	0·373	0·438	75	4·20	2·43	0·0323
50	0·373	0·447	50	4·20	1·60	0·0320
25	0·373	0·424	25	2·80	0·815	0·0326

appreciable, while the larger quantities of electricity are those corresponding to the attainment of the stationary state.

The interesting result which clearly emerges is that in the formation reaction the yield of hydrogen peroxide is independent of the volume of the anolyte, but the rate of the decomposition reaction is apparently proportional to the *concentration* of peroxide, so that in the stationary state it is the concentration of peroxide, not its absolute amount, which becomes constant.

Surface area and stirring. A large number of early observations suggested that the hydrogen peroxide was initially formed immediately under the glow-spot and diffused both laterally across the surface and inwards into the bulk of the electrolyte. The local concentration of peroxide in the region of the glow-spot is therefore higher than in the bulk of the solution, and, since the decomposition reaction depends on the concentration of peroxide, any factor tending to favour diffusion from the glow-spot would be expected to raise the yield of peroxide obtained in the stationary state. In conformity with this it was found that, while increase of surface area of anolyte and stirring had no appreciable effect on the yield of hydrogen peroxide for the passage of a small quantity of electricity, *i.e.*, while the formation reaction is predominating, these factors increased the stationary concentration of peroxide attained when a large quantity of electricity was passed. A selection of results is given in Table 3. In unstirred electrolytes,

TABLE 3. *Influence of surface area and stirring.*

Surface area (sq. cm.)	Quantity of electricity (10^{-3}F)	H_2O_2 formed (10^{-3} equiv.)	Surface area (sq. cm.)	Quantity of electricity (10^{-3}F)	H_2O_2 formed (10^{-3} equiv.)	H_2O_2 concn. (N)
10	0·373	0·414	10	2·80	1·04	0·2008
19	0·373	0·447	19	2·80	1·54	0·0308
38	0·373	0·445	38	2·80	1·59	0·0318
10 stirred	0·373	0·433	10 stirred	2·80	1·60	0·0320
19 stirred	0·373	0·440	19 stirred	2·80	1·65	0·0330

the introduction of any large obstruction in the surface was found, as would be expected, to decrease the stationary concentration of peroxide attained. The effect appears to be a purely mechanical one of hindering diffusion; no specific wall reactions seem to occur since on packing the anolyte loosely with glass wool the results were not appreciably affected.

Influence of Factors affecting the Discharge.—Electrode distance. In Table 4 are shown the results of a series of experiments in which the distance of the anode from the electrolyte surface was varied from 0·1 to 2·0 cm., standard conditions being otherwise employed.

It is seen that variation of electrode distance does not apparently affect the yield of hydrogen peroxide appreciably for the passage of either small or large quantities of electricity, until the electrode is brought within 0·25 cm. of the surface: a slight increase in the amount of hydrogen peroxide is then found.

TABLE 4. *Influence of electrode distance.*

Distance (cm.)	Voltage (V)	H_2O_2 formed (10^{-3} equiv.) $0·373 \times 10^{-3}$F	$2·80 \times 10^{-3}$F	Distance (cm.)	Voltage (V)	H_2O_2 formed (10^{-3} equiv.) $0·373 \times 10^{-3}$F	$2·80 \times 10^{-3}$F
2·0	700	0·451	1·52	0·5	580	0·447	1·54
1·5	680	0·432	1·49	0·25	540	0·488	1·67
1·0	620	0·446	1·51	0·1	520	0·489	1·74
0·75	600	0·434	1·49				

Shape and nature of electrode. To see if the results were dependent in any way on the shape, size, or nature of the electrode a series of experiments was carried out under standard conditions, with platinum electrodes in the form of a vertical wire, an L-shaped wire with the lower arm parallel to the liquid surface, and with ring and disc electrodes also parallel to the surface; vertical rod electrodes of tungsten, nickel, copper, nichrome, and graphite were also tried. The results are summarised in Table 5 and it is seen that none of these factors appreciably

TABLE 5. *Influence of shape, size, and nature of electrode.*

Electrode	H_2O_2 formed (10^{-3} equiv.) $0·373 \times 10^{-3}$F	$2·80 \times 10^{-3}$F	Electrode	H_2O_2 formed (10^{-3} equiv.) $0·373 \times 10^{-3}$F	$2·80 \times 10^{-3}$F
Pt: Wire	0·447	1·54	Pt	0·447	1·54
L-shaped wire	0·450	1·53	W	0·456	1·51
Ring	0·442	1·50	Ni	0·447	1·58
Disc	0·475	1·47	Cu	0·441	1·48
			Nichrome	0·458	1·52
			C	0·430	1·29

affected the results obtained. The graphite electrode tended to disintegrate and fragments of carbon fell into the electrolyte, probably bringing about some catalytic decomposition of the peroxide.

Nature of gas. To ascertain whether the nature of the gas present in the apparatus would influence the process occurring, experiments were carried out under the usual conditions with different gases present. In the first of two series all air in the apparatus was displaced by the

gas to be studied and then electrolysis was carried out in the usual way; in a second set a current of the gas was also blown continuously across the discharge during the electrolysis. The results are given in Table 6. The nature of the gas present has surprisingly little influence on the

TABLE 6. *Influence of nature of gas.*

	Gas	H_2O_2 formed (10^{-3} equiv.) 0.373×10^{-3}F	2.80×10^{-3}F		Gas	H_2O_2 formed (10^{-3} equiv.) 0.373×10^{-3}F	2.80×10^{-3}F
Static :	Air	0·447	1·54	Flowing :	Air ...	0·499	1·65
	N_2	0·448	1·52		N_2	0·476	1·64
	O_2	0·465	1·58		O_2	0·514	1·66
	H_2	0·411	1·50		H_2 ...	0·424	1·62
	N_2O	0·427	1·53		N_2O ...	0·479	1·66

amount of hydrogen peroxide formed; with oxygen the amount is somewhat higher, and with hydrogen rather lower, than the average, but the differences are not substantial. With the gas flowing across the discharge there is a general tendency for the yield of hydrogen peroxide to be somewhat greater, but this may well be an incidental effect due to the higher pressure in the region of the discharge and to some stirring of the electrolyte surface. The fact that the nature of the gas has so little effect supports the idea that the discharge is essentially one in water vapour; this is not unlikely since the local temperature of the liquid under the glow spot must be relatively high.

Pressure. Experiments were carried out under the usual standard conditions at different pressures of air, and the results are summarised in Table 7. Some loss of hydrogen peroxide

TABLE 7. *Influence of pressure.*

Pressure (mm.)	Voltage (v)	H_2O_2 formed (10^{-3} equiv.) 0.373×10^{-3}F	2.80×10^{-3}F	Pressure (mm.)	Voltage (v)	H_2O_2 formed (10^{-3} equiv.) 0.373×10^{-3}F	2.80×10^{-3}F
150	660	0·477	1·56	50	580	0·447	1·54
100	620	0·459	1·57	35	560	0·429	1·46
75	600	0·448	1·58	25	550	0·415	1·16

may occur at the lowest pressures by boiling of the solution; apart from this the effect of pressure seems to be relatively slight, there being some tendency for the amount of hydrogen peroxide formed to increase with rise of pressure.

Influence of Factors affecting the Solution.—Nature and pH *of electrolyte.* The formation of hydrogen peroxide and its dependence on quantity of electricity passed were comprehensively investigated, a wide variety of inert electrolytes being used, both stirred and unstirred, under standard conditions. The essential features of the results are summarised in Table 8. The initial yield of hydrogen peroxide in equiv./faraday has been found from the slope of the tangent to the initial section of each formation curve.

TABLE 8. *Influence of nature of electrolyte.*

Electrolyte (0·05M)	Approx. pH	Initial yield of H_2O_2 (equiv./F) Unstirred	Stirred	Stationary concn. of H_2O_2 (N) Unstirred	Stirred
NaOH	13—12	0	—	0	—
Na_2CO_3	11	0	—	0	—
$Na_2B_4O_7$	9	—	—	0·013	—
$NaHCO_3$	8	1·9	1·8	0·033	0·040
Na_2HPO_4	7	1·5	1·3	0·032	0·040
K_2SO_4	7—2	1·3	1·3	0·032	0·040
H_2SO_4	1	1·1	1·1	0·022	0·028

In strongly alkaline solutions no hydrogen peroxide can be detected after electrolysis, but in all other solutions the formation of hydrogen peroxide and its decomposition seem to follow essentially the same path, independently of the nature of the electrolyte. Over the pH range 8—2 the stationary concentration of hydrogen peroxide attained is substantially the same although the initial yield of hydrogen peroxide seems to increase somewhat with rising pH; similar results were also found when the electrolyte was a heterogeneous buffer (approx. pH 6 or 4) made by partly precipitating the metallic hydroxides from zinc and aluminium sulphates. At pH's 1 and 9 the stationary concentrations of hydrogen peroxide drop appreciably. The addition of catalysts for hydrogen peroxide decomposition such as $MnSO_4$, $CuSO_4$, $FeSO_4$, and $CoSO_4$ at 0·01M-concentration to a 0·05M-K_2SO_4 electrolyte was found to decrease somewhat the amount of hydrogen peroxide formed, but the effect was relatively slight.

Concentration. Increase of concentration of the electrolyte was found in general to raise

both the initial yield of hydrogen peroxide and the stationary concentration attained. This is illustrated by the results in Table 9 obtained with a sodium dihydrogen phosphate electrolyte under standard conditions. The effect appeared to be independent of the chemical nature of the electrolyte, and it is noteworthy that increase of concentration beyond a certain point had no further influence.

TABLE 9. *Influence of concentration.*

Concn. of NaH_2PO_4 (M)	0·1	0·2	0·5	1·0
Initial yield of H_2O_2 (equiv./F)	1·5	1·6	1·9	1·9
Stationary concn. of H_2O_2 (N)	0·033	0·040	0·048	0·048

TABLE 10. *Influence of temperature.*

Average temp. of electrolyte (approx. only)	40°	30°	20°
H_2O_2 formed (10^{-3} equiv.) $0·373 \times 10^{-3}$F	0·481	0·431	0·417
$2·80 \times 10^{-3}$F	2·05	2·12	2·43

Temperature. As has been mentioned, control of temperature in the electrolysis is very difficult, but some experiments were carried out with a stirred solution of 0·05M-disodium

FIG. 3. *Glow-discharge electrolysis of hydrogen peroxide.*

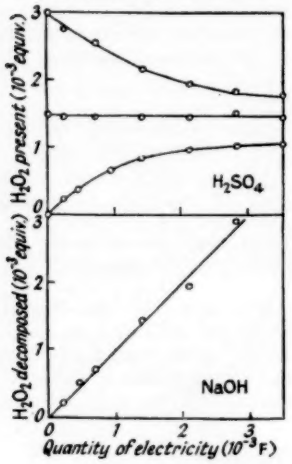
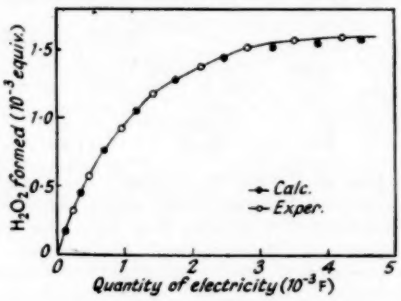


FIG. 4. *Formation of hydrogen peroxide : calculated and experimental values.*



hydrogen phosphate and a pressure of 150 mm., the average bulk temperature being maintained at different values by altering the cooling-bath; the results are given in Table 10. While too much significance should not be attached to these results, it does appear that rise of temperature increases somewhat the initial yield of hydrogen peroxide but decreases the stationary concentration attained.

Decomposition of Hydrogen Peroxide by Glow-discharge Electrolysis.—The decomposition of hydrogen peroxide by glow-discharge electrolysis was studied in 0·05M-H_2SO_4, -Na_2HPO_4, and -NaOH electrolytes by starting with solutions containing different initial amounts of hydrogen peroxide, and finding that present after the passage of various quantities of electricity, standard conditions being employed. Typical results are illustrated in Fig. 3.

In H_2SO_4 and Na_2HPO_4 electrolytes, the hydrogen peroxide present changed in amount on electrolysis until the concentration approached the previously found stationary values, whereafter it remained constant. In the NaOH electrolyte, continuous decomposition of the hydrogen peroxide occurred, the amount decomposed being proportional to the quantity of electricity passed and corresponding approximately to 1 equiv./faraday.

DISCUSSION

The experimental results have shown that, contrary to what might have been expected, electrolysis of inert aqueous solutions with a glow-discharge anode leads to relatively simple and reproducible results. There appears to be an initial formation of hydrogen peroxide

followed by a subsequent decomposition, the rate of both reactions depending on the current passing, and a simple interpretation which will cover many features of the process can be reached on a purely electrolytic basis. Since it seems improbable that electrons could be emitted directly from the surface of the liquid electrolyte, the current must be conveyed by positive gaseous ions which are driven into the liquid from the gas phase and subsequently discharged, and, as has been mentioned previously, it seems likely that the discharge is primarily one through water vapour. We have no certain knowledge of the nature of the ions present in ionised water vapour at pressures corresponding to those used in the present work, but observations at much lower pressures made by use of mass spectrometer have shown that under these conditions the main positive ion present is H_2O^+, with substantial amounts of OH^+, smaller quantities of H^+ and H_3O^+, and trifling amounts of other ions (see Barton and Bartlett, *Phys. Review*, 1928, **31**, 823; Smyth and Mueller, *ibid.*, 1933, **43**, 116; Mann, Hustrulid, and Tate, *ibid.*, 1940, **58**, 340). If it is assumed that the main ions carrying the current in the present work are the H_2O^+ and OH^+ ions, then on entry of these into the solution the following simple reactions might occur :

$$H_2O^+_{gas} + H_2O_{liq.} \longrightarrow OH + H_3O^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (a)$$

$$H_2O^+_{gas} + OH^-_{liq.} \longrightarrow OH + H_2O \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (b)$$

$$OH^+_{gas} + OH^-_{liq.} \longrightarrow 2OH \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (c)$$

$$OH^+_{gas} + H_2O_{liq.} \longrightarrow 2OH + H^+ \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (d)$$

Each of these reactions leads to the formation of the OH radical as the primary species produced in solution, the yield being 1 equiv. of OH per faraday for reactions (*a*) and (*b*), and 2 equiv. of OH per faraday for reactions (*c*) and (*d*); in addition each reaction leads to the development of 1 equiv. of acid for each faraday passed. If then the OH radicals initially formed dimerise to give hydrogen peroxide

$$2OH \longrightarrow H_2O_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (e)$$

an initial yield of 1—2 equivs. of hydrogen peroxide per faraday would be expected. As the hydrogen peroxide accumulates in the electrolyte, however, interaction with OH radicals must occur as postulated in the well-known Haber–Weiss mechanism

$$H_2O_2 + OH \longrightarrow H_2O + HO_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (f)$$

and decomposition of the peroxide to water and oxygen will follow. At any time, therefore, the rate of increase in the amount of hydrogen peroxide will be given by an equation of the form

$$\frac{d(H_2O_2)}{dt} = a \cdot \frac{I}{F} - a \cdot \frac{I}{F} k[H_2O_2] \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where (H_2O_2) is the amount (in equiv.) of hydrogen peroxide and $[H_2O_2]$ is its concentration, a is the yield of the primary species OH per faraday, I is the current, and k is a coefficient for the decomposition reaction. On integration and application of the condition that there is no hydrogen peroxide present at the start of electrolysis, the equation becomes

$$(H_2O_2) = V(1 - e^{-\frac{akq}{V}})/k \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (2)$$

where q is the quantity of electricity in faradays and V is the volume of the solution.* Two special cases of the application of this equation are apparent : when q is small $(H_2O_2) \simeq aq$, *i.e.*, the amount of hydrogen peroxide is proportional to the quantity of electricity; when q is large, $(H_2O_2) = V/k$, *i.e.*, $[H_2O_2] = 1/k$ and a stationary concentration of the peroxide is attained. Equation (2) has been tested in numerous cases by inserting experimental values of a and V/k and it fits the experimental observations remarkably well. In Fig. 4, for example, are shown the experimental and calculated

* An equation somewhat similar in form has been deduced by Klemenc.

points for the electrolysis of 0·05M-disodium hydrogen phosphate under standard conditions.

The failure to obtain hydrogen peroxide in strongly alkaline electrolytes is readily understood from the electrolytic standpoint. A recent investigation (Hickling and Wilson, *J. Electrochem. Soc.*, 1951, **98**, 425) has shown that in alkaline solution hydrogen peroxide is very readily decomposed at an anode by discharge of the perhydroxyl ion

$$HO_2^- - 2e \longrightarrow H^+ + O_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (g)$$

and the present work has also shown that hydrogen peroxide is quantitatively and continuously decomposed in alkaline solution by a glow-discharge anode, probably by the same reaction; in the light of these observations no appreciable amount of hydrogen peroxide would be expected to accumulate in the glow-discharge electrolysis of alkaline electrolytes.

The main features of the glow-discharge electrolysis and the initial formation of hydrogen peroxide in amounts rather greater than those expected from Faraday's laws can be fairly well explained therefore on a simple electrolytic view. The fact that the initial yield of hydrogen peroxide is greater than 1 equiv./faraday implies that some reduction product must be formed also, and analysis of the gas present in the cell showed this reduction product to be hydrogen. Determination of all the products, gaseous and in solution, showed that throughout electrolysis the yield in equivalents of $H_2O_2 + O_2 - H_2$ was equal to the quantity of electricity passed in faradays; in the later stages of electrolysis no hydrogen remains in the cell gas since it is removed by combination with oxygen to give water in the gas phase.

On points of detail the above explanation is less satisfactory. It is not clear, for example, why the initial yield of hydrogen peroxide should increase with concentration of electrolyte and with rise of pH over the range 2—8, and a yield of 1·9 equiv./faraday would imply that nearly all the current was being carried to the electrolyte surface by gaseous OH^+ ions, which seems very unlikely. It is of course entirely possible that entry of positive gaseous ions into the solution may bring about dissociation of water molecules by either ionisation or excitation in the general way now attributed to ionising radiations of many types (cf. Dainton, *Ann. Reports*, 1948, **45**, 5). The primary species leading to the formation of hydrogen peroxide would again be the OH radical and subsequent reactions would be the same, but the yield of hydrogen peroxide might be considerably greater than that expected from simple electrolysis. In the present work, however, the importance of quantity of electricity as the main variable, and the substantial independence of the results of factors affecting the electrical discharge, favour the view that the hydrogen peroxide arises mainly, if not solely, by simple electrolysis.

The present results carry some important implications for the mechanism of the discharge of hydroxyl ions at solid anodes in ordinary electrolysis. Much work on electrolytic oxidation has suggested that hydrogen peroxide may well be an intermediate between the discharge of the hydroxyl ion and the formation of oxygen and water (see Glasstone and Hickling, *Chem. Reviews*, 1939, **25**, 407), but hydrogen peroxide can rarely be detected in these circumstances. In view, however, of its further decomposition by interaction with OH radicals, and the high local concentrations at a solid surface, this is not surprising. It has been suggested (Hickling, *Quart. Reviews*, 1949, **3**, 95) that a possible mechanism for the electrode reaction is

$$\begin{aligned} OH^- - e &\longrightarrow OH \\ 2OH &\longrightarrow H_2O_2 \\ OH + H_2O_2 &\longrightarrow H_2O + HO_2 \\ OH + HO_2 &\longrightarrow H_2O + O_2 \end{aligned}$$

and the present work seems to lend some support to this general idea.

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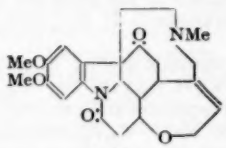
687. *The Isolation of Novacine, an Alkaloid from* Strychnos Nux-vomica, *L. and its Identification as* N-*Methyl*-sec.-pseudo*brucine.*

By W. F. Martin, H. R. Bentley, J. A. Henry, and F. S. Spring.

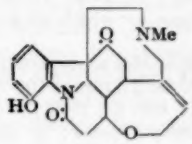
N-Methyl-*sec.-pseudo*brucine (novacine) has been identified as a minor alkaloid of *Strychnos Nux-vomica*, L.

From residues obtained during the purification of crude brucine sulphate from *Strychnos Nux-vomica* seeds, a new alkaloid has been isolated for which the name novacine is proposed. Novacine occurs together with vomicine in a fraction separated from strychnine and brucine by taking advantage of the solubility of the hydrochlorides of the two last-named alkaloids in chloroform. Thereafter novacine and vomicine can be conveniently separated as their hydrogen tartrates which have markedly different solubilities in water.

Analyses of novacine and of several of its crystalline derivatives established the formula $C_{24}H_{28}O_5N_2$ for the alkaloid and this led to its identification as *N*-methyl-*sec.-pseudo*-brucine (I) previously obtained by Leuchs and Tessmar (*Ber.*, 1939, **72,** 965) from *pseudo*-brucine by the action of methyl iodide.



(I)



(II)

The relation between *N*-methyl-*sec.-pseudo*brucine (I) and vomicine (II) has recently been established by Robinson (cf. Robinson, "Progress in Organic Chemistry," Vol. I, p. 15, Butterworth's Scientific Publns., London, 1952; Bailey and Robinson, *Nature*, 1948, **161,** 433). Novacine is thus a second alkaloid of the vomicine type. It occurs to an approximately equal extent with the latter in the residues we have examined and its isolation suggests that further search may reveal the presence of other alkaloids related to vomicine.

Experimental

Isolation of Novacine Hydrochloride.—The alkaloid mixture from nux-vomica beans from which most of the strychnine had been removed gave a crude brucine sulphate. Purification of this gave pure brucine sulphate, a small quantity of strychnine, and a dark resinous alkaloidal residue, which contained brucine, a small amount of strychnine, and the minor alkaloids of *S. Nux-vomica*.

The resinous mixture (1500 g.) was dissolved in water (5 l.) containing sufficient hydrochloric acid to make the final solution slightly acid, and the mixture diluted with water (15 l.). The solution was clarified by adding with stirring an aqueous solution of aluminium sulphate (25 g.), followed by sufficient ammonia to make the solution nearly neutral. The mixture was kept overnight, then filtered, and the mixed alkaloids were precipitated by the addition of dilute aqueous ammonia. The gummy precipitate was collected by decantation, washed with water and dissolved with heating, in water (approx. 3 l.) containing sufficient hydrochloric acid (20%) to neutralise the alkaloids. One-half of the equivalent volume of hydrochloric acid was added and the cooled solution extracted with chloroform (20 × 2500 ml.) to remove brucine and strychnine hydrochlorides. Small amounts of solid (novacine hydrochloride) separating from the chloroform phase towards the end of the extraction were collected. The dark aqueous solution was basified with ammonia solution (10—15%) and kept overnight. The dark-brown granular alkaloids (150 g.) were collected, washed with water, and dissolved in water (200 ml.) containing sufficient tartaric acid to make the solution acid to litmus. Ethanol (100 ml.) was added and the mixture kept overnight. The crystalline solid (45 g.) was

collected and treated with ammonia solution, and the crystalline base collected and recrystallised from acetone, to give vomicine as prisms, m. p. 281° alone or mixed with an authentic specimen, $[\alpha]_D^{20}$ +84° (*c*, 0·55 in ethanol) (Found: C, 69·7; H, 6·7. Calc. for $C_{22}H_{24}O_4N_2$: C, 69·5; H, 6·4%).

The aqueous-alcoholic mother-liquor was concentrated, cooled, diluted to 200 ml. with water, and basified with ammonia solution (15%). After several days the brown granular alkaloid (70 g.) was collected, washed with water, and dissolved in water (100 ml.) containing sufficient hydrochloric acid (*d*, 1·18) to give a slightly acid solution. The solution was concentrated to a small volume and set aside for several days, and the partly crystalline mixture triturated with 90% ethanol. The crystalline solid, novacine hydrochloride (30·0 g.), was collected, washed with 90% ethanol, and dried.

Novacine.—An aqueous solution of the hydrochloride was treated with ammonia solution. The oil separating rapidly solidified. For analysis a specimen was converted into the hydrogen tartrate by crystallisation from a concentrated aqueous solution containing tartaric acid (1 mol.), and the salt was recrystallised six times from water and decomposed with aqueous ammonia; the free alkaloid was collected, dried, recrystallised twice from ethyl acetate, and dried for 3 hours at 120°/0·2 mm. Novacine was thereby obtained as prisms, m. p. 231—232°, $[\alpha]_D^{20}$ −17·7° (*c*, 5·0 in chloroform) (Found: C, 68·0, 68·2, 68·05; H, 6·8, 6·7, 6·8; N, 6·9, 6·9, 7·0. Calc. for $C_{24}H_{28}O_5N_2$: C, 68·0; H, 6·65; N, 6·6%). A specimen of *N*-methyl-*sec.*-*pseudo*brucine prepared by Leuchs and Boit's method (*Ber.*, 1940, **73**, 885) crystallised from ethyl acetate as prisms, m. p. 231—232° alone or mixed with a specimen of novacine, $[\alpha]_D^{20}$ −18·2° (*c*, 1·8 in chloroform) (Found: C, 68·3; H, 6·7%). A comparison of the infra-red absorption spectra of the two specimens, for which we are indebted to Professor E. R. H. Jones, F.R.S., confirmed their identity.

Novacine hydrochloride separates from ethanol as prismatic needles, m. p. 229—230° (Found, in a specimen dried for 3 hours at 100°/0·2 mm.: C, 59·8; H, 6·5; Cl, 7·4. $C_{24}H_{28}O_5N_2,HCl,H_2O$ requires C, 60·2; H, 6·5; Cl, 7·4%). *Novacine picrate* separates from ethanol as yellow prisms, m. p. 250° (decomp.) (Found: C, 55·2; H, 4·8; N, 10·7. $C_{24}H_{28}O_5N_2,C_6H_3O_7N_3$ requires C, 55·2; H, 4·8; N, 10·7%). *Novacine hydrogen tartrate* separates from water as prisms, m. p. 235° (decomp.) (Found: C, 58·0; H, 5·9; N, 5·1. $C_{24}H_{28}O_5N_2,C_4H_6O_6$ requires C, 58·6; H, 6·0; N, 4·9%). *Novacine hydrogen oxalate* crystallises from water as prisms, m. p. 246° (decomp.) (Found, in a specimen dried for 30 minutes at 140°/0·2 mm.: C, 58·5; H, 5·7; N, 5·7. $C_{24}H_{28}O_5N_2,C_2H_2O_4,H_2O$ requires C, 58·7; H, 6·1; N, 5·3%).

Dihydronovacine.—Hydrogenation of novacine by Leuchs and Tessmar's method (*loc. cit.*) and crystallisation of the product from ethyl acetate gave dihydronovacine as prisms, m. p. 237—238°, $[\alpha]_D^{20}$ +168° (*c*, 2·4 in chloroform) (Found: C, 67·7; H, 6·9; N, 6·7. Calc. for $C_{24}H_{30}O_5N_2$: C, 67·6; H, 7·1; N, 6·6%). A specimen of dihydro-*N*-methyl-*sec.*-*pseudo*-brucine prepared similarly had m. p. 237—238° alone or mixed with a specimen of dihydronovacine, $[\alpha]_D^{20}$ +168° (*c*, 2·6 in chloroform).

Analyses were by Dr. A. C. Syme and Mr. Wm. McCorkindale. Acknowledgment is made to the Governors of The Royal Technical College, Glasgow, for the award of the C. S. Crawford and Walter Duncan Research Scholarships (to J. A. H.) and to the Directors of T. & H. Smith. Ltd., Edinburgh, for facilities which made this investigation possible.

T. & H. Smith, Ltd., Edinburgh.
The Royal Technical College, Glasgow.

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688. *Interaction of Naphthalene and Maleic Anhydride through the Agency of Aluminium Chloride.*

By G. Baddeley, G. Holt, S. M. Makar, and (Miss) M. G. Ivinson.

A mixture of β-1- and β-2-naphthoylacrylic acids is obtained in good yield only in the absence of excess of dissolved or of solid aluminium chloride; the acids are readily separated by crystallisation from ethylene chloride. They isomerise to 3-keto-4 : 5-benzindane-1-carboxylic acid (III) and 1-keto-4 : 5-benzindane-3-carboxylic acid (IV) respectively in the presence of hydrogen chloride and excess of aluminium chloride. In the past, the former has been mistaken for 3-ketoperinaphthane-1-carboxylic acid (VII) and also for β-2-naphthoylacrylic acid; an authentic sample of β-2-naphthoylacrylic acid has not been obtained previously. Decarboxylation of the ketobenzindanecarboxylic acids affords ready access to 4 : 5-benzindan-3- and -1-one (V and VI). The reactions are discussed.

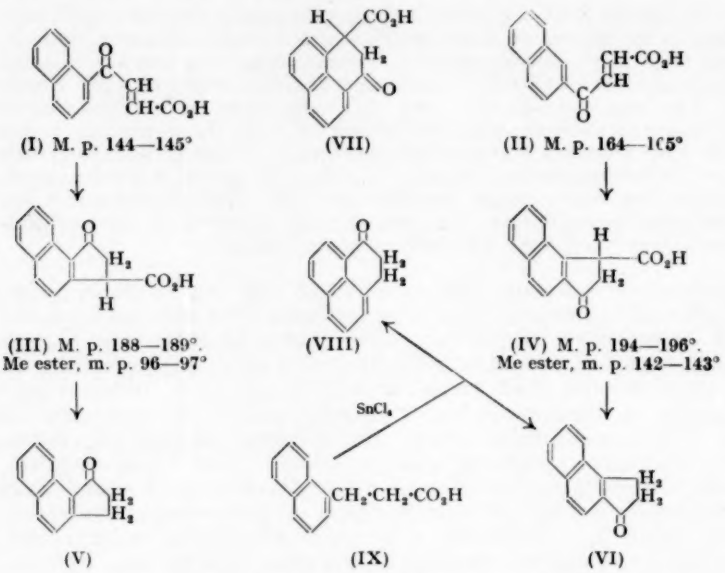
The precautions necessary to avoid side-reactions and thus to obtain good yields of β-aroylacrylic acids by interaction of an aromatic hydrocarbon with maleic anhydride in the presence of aluminium chloride have been enumerated in an earlier paper (*J.*, 1952, 3289); they demand absence of excess of, or undissolved, chloride and have now been successfully applied in the preparation of β-1- and β-2-naphthoylacrylic acids. Whereas acid chlorides and anhydrides of monobasic acids, when fully engaged by aluminium chloride in methylene or ethylene chloride as solvent, effect mainly α-substitution in naphthalene (*J.*, 1949, 998), yet phthalic, succinic and maleic anhydrides, under similar conditions, provide considerable β-substitution; this difference will be discussed in a further communication. The resulting mixtures of keto-acids can be separated by fractional crystallisation (*e.g.*, see Barnett and Campbell, *J.*, 1935, 1031) or by fractional precipitation by gradual addition of mineral acid to an aqueous solution of the sodium salts (see, *e.g.*, Newman, Taylor, Hodgson, and Garrett, *J. Amer. Chem. Soc.*, 1947, **69**, 1784).

The complex of maleic anhydride with aluminium chloride (2 mols. as $AlCl_3$), in solution in methylene or ethylene chloride, provides a ready reaction when decanted from undissolved halide into a solution of naphthalene in the same solvent; the resulting β-1- and β-2-naphthoylacrylic acids are conveniently separated by recrystallisation from ethylene chloride. Each is golden-yellow, affords a red solution in concentrated sulphuric acid, decolorises bromine in carbon tetrachloride, and is oxidised to the corresponding naphthoic acid by cold permanganate.

β-2-Naphthoylacrylic acid (II), in a molten mixture of aluminium and sodium chlorides at *ca.* 100°, affords a saturated isomeric acid which melts with decomposition at 194—196°; the following evidence shows it to be 1-keto-4 : 5-benzindan-3-carboxylic acid (IV). The product of decomposition at the melting point has the same properties, m. p. 120—121° and oxime of m. p. 226—227°, as has one of the products of interaction of β-1-naphthylpropionic acid (IX) and anhydrous stannic chloride (Cook and Hewitt, *J.*, 1934, 365) and is 4 : 5-benzindan-1-one (VI) as reduction provides 4 : 5-benzindane which was identified by its picrate and addition compound with 1 : 3 : 5-trinitrobenzene (*J.*, 1952, 807); Cook and Hewett (*loc. cit.*) were uncertain whether their product was (VI) or perinaphthan-1-one (VIII).

Similarly, β-1-naphthoylacrylic acid (I) affords a saturated isomeric acid, m. p. 188—189°; this provides 4 : 5-benzindan-3-one (V) on decarboxylation and is therefore 3-keto-4 : 5-benzindan-1-carboxylic acid (III). The isomerisation of β-1-naphthoylacrylic acid through the agency of aluminium chloride at 120—140° has been described previously (B.P. 273,321/1927; U.S.P., 1,702,002/1929); the product is identical with ours, but has been incorrectly referred to as dihydrophenalone-7-carboxylic acid (3-ketoperinaphthane-1-carboxylic acid) (VII) (Thomas, "Anhydrous Aluminium Chloride in Organic Chemistry," Reinhold Publ. Corp., New York, 1941, p. 492). The above isomerisations of β-1- and β-2-naphthoylacrylic acids have also been realised in the presence of hydrogen chloride and

excess of aluminium chloride in solutions in methylene chloride at room temperature (see Experimental); excess of or undissolved aluminium chloride must therefore be avoided, as in our procedure, in the preparation of naphthoylacrylic acids. In the past this precaution has not been taken and, in consequence, some confusion has arisen; we have been obliged to repeat much of the earlier work.



Oddy (*J. Amer. Chem. Soc.*, 1923, **45**, 2156) gradually added powdered aluminium chloride to a solution of naphthalene and maleic anhydride in benzene and subsequently heated the mixture at 60—70° for four hours. A product, m. p. 189—190° (methyl ester, m. p. 94—95°), was isolated and did not decolorise bromine in acetic acid solution; it is (III), but has been referred to as β-2-naphthoylacrylic acid (II). A small amount of a substance, m. p. 158—159°, was also isolated but was not investigated; it was an impure sample of β-2-naphthoylacrylic acid (m. p. 164—165°). Bogert and Ritter (*ibid.*, 1925, **47**, 526) modified Oddy's procedure; the temperature was kept below 20° during the addition of the chloride and the reaction mixture was refluxed on the steam-bath until evolution of hydrogen chloride was complete. The product was crystallised from toluene and afforded two acids, m. p. 150·2° and 188° respectively, which are referred to as β-1- and β-2-naphthoylacrylic acid respectively. The former is impure β-2-naphthoylacrylic acid and melts at 160—162° after further recrystallisation from ethylene chloride; the latter is (III). Preparation of β-1-naphthoylacrylic in nitrobenzene as solvent has been described (U.S.P. 1,702,002) and we have confirmed it; the yield is 35% and we were unable to isolate any β-2-naphthoylacrylic acid.

As ease of cyclisation of β-aroylacrylic acids is directly related to ease of electron release from the aromatic ring (*e.g.*, the rate of reaction increases with the number of methyl groups attached to this ring), and as the ketone group in β-1-naphthoylacrylic acid ensures that the electron density at the 2- is less than that at the 8-position, ring closure in this instance might be expected to be effected at the latter. It occurs exclusively at the 2-position, as does ring closure of α-naphthyl vinyl ketones (Mayer and Müller, *Ber.*, 1927, **60**, 2278), and appears all the more remarkable by comparison with the cyclisation of β-1-naphthylpropionic acid which occurs at the 8- as well as at the 2-position even though the latter is not encumbered by a carbonyl group in the 1-position. We have observed (*loc. cit.*) that cyclisation of β-aroylacrylic acids is greatly assisted by an *o*-methyl group and believe

that this is due to steric interaction between bulky *o*-substituent on the one hand and the carbonyl group in association with aluminium chloride on the other; this would hinder resonance interaction between the carbonyl group and the aromatic ring and render the latter more susceptible to electrophilic attack. It is possible that the 8-position in β-1-naphthoylacrylic acid acts as a bulky *o*-substituent and aids ring closure at the 2-position.

Isomerisation of β-2-naphthoylacrylic acid to 1-keto-4 : 5-benzindane-3-carboxylic acid is consistent with the formation of 1 : 2-benzanthraquinone from *o*-2-naphthoylbenzoic acid (Brand and Trebing, *Ber.*, 1923, **56**, 2547); ring closure in such instances usually occurs at the 1- rather than at the 3-position (cf. *J.*, 1950, 994; Buckley, *J.*, 1945, 561, 564).

Experimental

β-1- *and* β-2-*Naphthoylacrylic Acids*.—Aluminium chloride (280 g.) was gradually added to a stirred solution of maleic anhydride (98 g.) in methylene chloride (300 c.c.). The mixture was stirred for 0·5 hour and the solution was slowly decanted from a little undissolved aluminium chloride into a solution of naphthalene (128 g.) in methylene chloride (150 c.c.); reaction was very fast and the product was poured on ice. The organic layer was separated and shaken with concentrated hydrochloric acid; it deposited yellow crystals (108 g.), m. p. 135—155°, which were separated. The filtrate slowly deposited yellow crystals (56 g.), m. p. 120—130°, which afforded golden-yellow needles of β-1-naphthoylacrylic acid, m. p. 144—145° (Found : C, 74·2; H, 4·6. Calc. for $C_{14}H_{10}O_3$: C, 74·3; H, 4·4%), from glacial acetic acid or ethylene chloride. This product afforded α-naphthoic acid, m. p. and mixed m. p. 160—161°, by oxidation with potassium permanganate.

β-2-*Naphthoylacrylic acid* was the main constituent of the first batch of crystals and crystallised from ethylene chloride in golden-yellow plates, m. p. 164—165° (Found : C, 74·5; H, 4·6%). This, like β-naphthoic acid, is readily purified since its sodium salt is sparingly soluble in sodium carbonate solutions; it afforded β-naphthoic acid, m. p. and mixed m. p. 181—183°, by oxidation with permanganate.

Isomerisation of β-1-*Naphthoylacrylic Acid*.—This acid (9 g.) was gradually added to a molten mixture of aluminium chloride (90 g.) and sodium chloride (13·5 g.) at 115°. After an hour, the mixture was poured into ice and dilute hydrochloric acid, and the pale brown product was separated by filtration and extracted with boiling water; the extracts deposited colourless needles of 3-keto-4 : 5-benzindane-1-carboxylic acid (5·9 g.), m. p. 188—189° (Found : C, 74·6; H, 4·1%; equiv., 225. Calc. for $C_{14}H_{10}O_3$: C, 74·3; H, 4·4%; equiv., 226). The methyl ester crystallised from methanol in long colourless needles, m. p. 96—97° (Found : C, 74·6; H, 5·0. Calc. for $C_{15}H_{12}O_3$: C, 75·0; H, 5·0%). The acid was decarboxylated by copper chromite in quinoline at 170—180°; the catalyst was removed by filtration, quinoline was separated by extraction with acid, and the residue was distilled with steam. It afforded 4 : 5-benzindan-3-one, m. p. and mixed m. p. 101—103°.

Isomerisation of β-2-*Naphthoylacrylic Acid*.—Procedure was similar to that described above. The acid (5 g.) afforded 1-*keto*-4 : 5-*benzindan*-3-*carboxylic acid* (2·5 g.) which crystallised from glacial acetic acid in colourless crystals, m. p. 194—196° (decomp.) (Found : C, 74·2; H, 4·6%). The yield improved from 50 to 64% when isomerisation was effected at 90—95° for 1·5 hours. The methyl ester separated from methanol in needles, m. p. 142—143° (Found : C, 74·8; H, 4·9%). The acid readily decomposed at 200° and afforded 4 : 5-benzindan-1-one which crystallised from methanol in pale yellow needles, m. p. 120—121°. With concentrated sulphuric acid it provided a yellow solution with a green fluorescence. Reduction by the Clemmensen method afforded 4 : 5-benzindane (picrate, m. p. and mixed m. p. 108—109°; addition compound with 1 : 3 : 5-trinitrobenzene having m. p. and mixed m. p. 119—120°).

The isomerisations described above also occur in the presence of hydrogen chloride and excess of aluminium chloride in methylene chloride at room temperature.

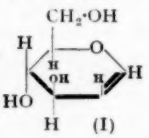
Faculty of Technology, Manchester University. [*Received, May 22nd*, 1952.]

689. *Deoxy-sugars. Part XXIV.* Conversion of* D-*Glucal into Furan Derivatives.*

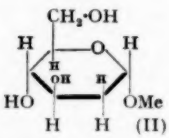
By F. Shafizadeh and M. Stacey.

D-Glucal on treatment with methanolic hydrogen chloride affords αβ-methyl-2-deoxy-D-glucoside and other substances amongst which 2-hydroxymethyl-5-methoxymethylfuran was identified. Some properties and derivatives of this compound are described.

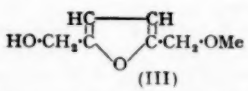
During previous investigations on deoxy-sugars (Overend, Shafizadeh, and Stacey, *J.*, 1951, 992) it was noted that treatment of D-galactal with methanolic hydrogen chloride afforded mainly α- and β-methyl-2-deoxy-D-galactosides, the yield of which decreased with increase of acid concentration. The reaction was complex since the optically active glycosidic products were invariably accompanied by an unidentified optically inactive liquid which absorbed bromine and possessed a methoxyl residue. We have found that a similar reaction takes place when D-glucal (I) is treated with 2% methanolic hydrogen chloride. From this reaction α-methyl-2-deoxy-D-glucopyranoside (II) may be isolated as previously reported by Hughes, Overend, and Stacey (*J.*, 1949, 2846); a residual liquid product obtained from the reaction afforded on fractionation one component as a homogeneous, mobile, and colourless syrup, which closely resembled in the above properties the unidentified product obtained from D-galactal. This compound having empirical formula of $C_7H_{10}O_3$ was identified as 2-hydroxymethyl-5-methoxymethylfuran (III) on the following evidence. The ultra-violet absorption spectrum was closely similar to that of furfuryl alcohol, showing a maximum absorption at 216 mμ which indicates the presence of a pair of conjugated double bonds (cf. Braude, *Ann. Reports*, 1945, **42**, 105). A crystalline 3 : 5-dinitrobenzoate was a useful characteristic derivative.



(I)



(II)



(III)

Hydrogenation using Raney nickel at room temperature resulted in absorption of 2 mols. of hydrogen and converted the liquid into tetrahydro-2-hydroxymethyl-5-methoxymethylfuran, the properties of which were in agreement with those recorded by Wiggins and Wood (*J.*, 1950, 1566) for a product obtained by treatment of 1 : 2-5 : 6-diepoxyhexane with sodium methoxide. This was a liquid and the above workers did not record the isolation of any crystalline derivative, so that further investigations were necessary to confirm its identity.

It was conveniently characterised by conversion into its *p*-nitrobenzoate. With alkaline potassium permanganate it afforded a potassium monocarboxylate which was converted into a liquid methyl ester and then into a crystalline amide, by standard methods. Oxidation of the tetrahydro-alcohol with hot dilute nitric acid afforded oxalic acid and unidentified products. Finally, methylation by the liquid ammonia technique afforded tetrahydro-2 : 5-bismethoxymethylfuran having the same constants as the product prepared by Wiggins and Wood (*loc. cit.*) from tetrahydro-2 : 5-bishydroxymethylfuran.

These observations prove the nature of the hydrogenated product and thus the skeleton orientation of (III). Further, the conjugated double bonds which had been demonstrated by the absorption spectrum must be as in (III) since any other assignment would furnish an optically active compound.

2-Hydroxymethyl-5-methoxymethylfuran was found to be a very labile compound which was rapidly decomposed with charring by hot mineral acids. The hydrogenated product was, however, recovered unchanged after treatment with hot N-hydrochloric acid.

* Part XXIII, *J.*, 1952, 255.

Acid treatment of tetramethyl 1 : 2-glucoseen (Wolfrom, Wallace, and Metcalf, *J. Amer. Chem. Soc.*, 1942, **64**, 265) and tetramethyl fructofuranose (Haworth, Hirst, and Nicholson, *J.*, 1927, 1513) affords 5-methoxymethylfurfuraldehyde, which is closely related to (III). Although under controlled conditions the aldehyde is smoothly oxidised to 5-methoxymethylfuroic acid without the double bonds in the furan ring being affected, attempted oxidation of (III) produced only degradation products and unchanged starting material, evidently owing to the greater resistance of the hydroxymethyl group to the oxidising agent (permanganate).

Formation of 2 : 5-disubstituted furans from hexoses and their oxidation products is a well-known feature of carbohydrate chemistry (cf. Newth, *Adv. Carbohydrate Chem.*, 1951, **6**, 83). The mechanism of some of these transformations has been discussed by Isbell (*J. Res. Nat. Bur. Stand.*, 1944, **32**, 45) who attached special importance to enolisation during these reactions. The conversion of D-glucal into 2-hydroxymethyl-5-methoxymethylfuran is a similar reaction which emphasises the effect of the double bond in these transformations. Recently we have found that treatment of D-glucal with 5% sulphuric acid forms a dehydration product which contains a pair of conjugated double bonds as shown by its ultra-violet absorption spectrum and yet is optically active. This liquid compound which is a by-product in the preparations of 2-deoxyglucose and 2-deoxygalactose from the glycals will form the subject of a later communication. Various interesting liquid products from the acid treatment of arabinal and 2-deoxyglucose are also being examined.

Experimental

D-Glucal.—Triacetyl D-glucal (cf. Fischer, *Ber.*, 1914, **47**, 196) (64 g.) was dissolved in dry methanol (1 l.), and sodium (160 mg.) was added. The solution was kept at room temperature for 2 days, treated with carbon dioxide, and evaporated under diminished pressure. The dry residue was extracted with hot ethyl acetate. The combined extracts were concentrated, affording D-glucal (25 g.), m. p. 57—59°, $[\alpha]_D^{19}$ −8·0° (*c*, 1·88 in water).

Treatment of D-Glucal with Methanolic Hydrogen Chloride.—D-Glucal (45 g.) was treated with 2% methanolic hydrogen chloride (250 c.c.) at room temperature. After 18 hours the dark brown mixture was neutralised with silver carbonate, and the filtered solution was evaporated to a syrup which was repeatedly extracted with ether. The remaining syrupy residue on extraction with hot ethyl acetate afforded a solid product, which after several recrystallisations from the same solvent furnished α-methyl-2-deoxy-D-glucopyranoside (1·86 g.), m. p. 92—93°, $[\alpha]_D^{19\cdot5}$ +145° (*c*, 0·8 in methanol) [cf. Hughes, Overend, and Stacey (*loc. cit.*) who give m. p. 90—92° and $[\alpha]_D^{20}$ +135° (in water)]. The above ethereal extract on evaporation under reduced pressure afforded a liquid which was fractionally distilled under diminshed pressure. Further fractionation of the main distillate afforded *2-hydroxymethyl-5-methoxymethylfuran* (14·3 g.) as a homogeneous mobile liquid, b. p. 90° (bath-temp.), 47° (column-temp.)/0·3 mm., n_D^{17} 1·479 (Found : C, 59·1; H, 7·4; OMe, 21·6%; *M*, 147. $C_7H_{10}O_3$ requires C, 59·2; H, 7·0; OMe, 21·8%; *M*, 142). The product was highly unsaturated, absorbed bromine, and decolorised potassium permanganate solution. It had no optical activity and was soluble in water, alcohol, ether, and benzene. When brominated in chloroform solution it decomposed with much charring.

The 3 : *5-dinitrobenzoate* (prepared in pyridine at 0° during 20 hours) crystallised from methanol as pale yellow plates, m. p. 90°, $[\alpha]_D = \pm 0°$ (Found : C, 49·9; H, 3·8; N, 8·3. $C_{14}H_{12}O_8N_2$ requires C, 50·0; H, 3·6; N, 8·3%).

Hydrogenation of 2-Hydroxymethyl-5-methoxymethylfuran.—2-Hydroxymethyl-5-methoxymethylfuran (4·71 g.) in aqueous methanol (50 c.c.) was shaken at room temperature in an atmosphere of hydrogen at a slight over-pressure, with Raney nickel (1·2 g.). After 2 days, absorption of hydrogen (1·41 l.) was complete. The solution was then filtered and evaporated to a syrup from which tetrahydro-2-hydroxymethyl-5-methoxymethylfuran (4·37 g.) was obtained as a colourless, mobile syrup, b. p. 130—140° (bath-temp.)/12 mm., n_D^{18} 1·457 (Found : OMe, 21·5. Calc. for $C_7H_{14}O_3$: OMe, 21·2%). Wiggins and Wood (*loc. cit.*) give b. p. 159—164° (bath-temp.)/15 mm., n_D^{22} 1·4511. In pyridine (room temp., 16 hours; then at 0°, 3 days) it gave a p-*nitrobenzoate*, m. p. 59·5° (from ether) (Found : C, 57·1; H, 5·4; N, 4·8. $C_{14}H_{17}O_6N$ requires C, 56·9; H, 5·8; N, 4·7%).

Oxidation of Tetrahydro-2-hydroxymethyl-5-methoxymethylfuran.—(a) *With potassium permanganate.* Tetrahydro-2-hydroxymethyl-5-methoxymethylfuran (0·790 g.) was added to a

solution of potassium permanganate (1·58 g.) and potassium hydroxide (0·61 g.) in water (60 c.c.). After 18 hours at room temperature the brown mixture was neutralised with carbon dioxide and the filtered solution evaporated to dryness under diminished pressure. The residue was washed with ether to remove any unchanged material and then extracted with dry methanol. The extract was concentrated (10 c.c.) and then heated under reflux for 5 hours with excess of methyl iodide (10 c.c.). The solvents were evaporated and the residue extracted with warm ether. The residue of this extraction was re-treated with methanol and methyl iodide and the above procedure repeated. The combined ethereal extracts were evaporated to a syrup from which the crude methyl ester was obtained (0·27 g.) as a colourless syrup, b. p. 140° (bath-temp.)/12 mm., n_D^{18} 1·444. This product (0·200 g.) was dissolved in absolute methanol, and the solution saturated with ammonia and set aside for 18 hours at room temperature. Evaporation of the solvent gave a solid residue which on recrystallisation from ether afforded *tetrahydro-5-methoxymethylfuran-2-carboxyamide* (0·12 g.), m. p. 99—102° (Found: C, 52·2; H, 8·1; N, 8·6. $C_7H_{13}O_3N$ requires C, 52·8; H, 8·2; N, 8·8%).

(b) *With nitric acid.* Tetrahydro-2-hydroxymethyl-5-methoxymethylfuran (2·01 g.) in nitric acid (*d* 1·15; 30 c.c.) was heated at 100° for 2 hours. When the vigorous evolution of nitric fumes ceased, the solution was diluted with water and evaporated under diminished pressure. This procedure was repeated several times until most of the nitric acid had been evaporated; a mixture of syrup and crystals was obtained. This was filtered through a sintered-glass crucible, and washed with ether. Recrystallisation from moist ether afforded oxalic acid dihydrate (0·41 g.), m. p. 99°.

Methylation of Tetrahydro-2-hydroxymethyl-5-methoxymethylfuran.—The monomethoxy-compound (1·215 g.) was added to dry liquid ammonia (100 c.c.), and sodium (0·4 g.) was added in small pieces. The mixture was mechanically stirred under dry conditions for 2 hours and then methyl idodide (1·07 c.c.) was added. This procedure was repeated three times. When the liquid ammonia had evaporated the residue was extracted with chloroform. The extract was dried ($MgSO_4$) and the solvent removed under diminished pressure. From the crude product tetrahydro-2 : 5-bismethoxymethylfuran (0·74 g.) was obtained as a colourless mobile liquid, b. p. 90—94° (bath-temp.), 75° (column-temp.)/12 mm., n_D^{21} 1·4368 (Found: C, 60·1; H, 10·4; OMe, 38·4. Calc. for $C_8H_{16}O_3$: C, 60·0; H, 10·0; OMe, 38·7%). Wiggins and Wood (*loc. cit.*) give b. p. 90—95° (bath-temp.)/12 mm., $n_D^{19\cdot5}$ 1·4369.

This study was initiated with the co-operation of Dr. W. G. Overend, to whom thanks are due for his interest in this work. One of us (F. S.) also thanks the British Empire Cancer Campaign (Birmingham Branch) for the award of a grant.

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690. cyclo*Propanes. Part I. The Malonate Condensation with* 1 : 4-*Dibromobut-2-ene. A Convenient New Route to Vinyl*cyclo*propane Derivatives.*

By R. W. KIERSTEAD, R. P. LINSTEAD, and B. C. L. WEEDON.

Condensation of 1 : 4-dibromobut-2-ene with ethyl sodiomalonate gives mainly ethyl 2-vinyl*cyclo*propane-1 : 1-dicarboxylate (VI; R = Et) together with small amounts of the tetraesters (XII) and (XIII).

On catalytic hydrogenation of (VI; R = Et) both the double bond and the *cyclo*propane ring are reduced with formation of ethyl *n*-butylmalonate.

Molecular-refractivity data for (VI; R = Et) indicate electronic interaction between the vinyl group and the *cyclo*propane ring.

The mechanism of the malonate condensation is discussed.

WE recently required hex-3-ene-1 : 6-dicarboxylic acid for synthetical work. At first sight it seemed likely that the dimalonic ester corresponding to this could easily be prepared by interaction between ethyl sodiomalonate and the stable 1 : 4-dibromide of butadiene (1 : 4-dibromobut-2-ene). This looked all the more probable because Kepner, Winstein, and Young (*J. Amer. Chem. Soc.*, 1949, **71**, 115) have recently shown that primary

allyl halides condense with sodiomalonate by a normal bimolecular mechanism. Investigation showed that the reaction with dibromobutene took a different and much more interesting course, and we can now report a new and attractive method for the preparation of *cyclo*propane compounds.

When 1 : 4-dibromobut-2-ene is condensed with 2 mols. of sodiomalonate only a small amount of a tetracarboxylic ester fraction is produced. This is a mixture which is discussed later. The main product is a dicarboxylic ester, $C_{11}H_{16}O_4$, clearly formed by the replacement of one bromine atom by a malonate residue and the elimination of the other as hydrogen bromide. Hydrolysis of the ester gives the corresponding substituted malonic acid, $C_7H_8O_4$, as a crystalline solid which are decarboxylated above 140°. Both the ester and acid are easily hydrogenated over platinum, two mols. of hydrogen being taken up. The products are ethyl *n*-butylmalonate and the corresponding acid.

(I) $CH_2{:}CH{\cdot}CH{:}CH{\cdot}CH(CO_2R)_2$ $CH_3{\cdot}CH{:}CH{\cdot}CH{:}C(CO_2R)_2$ (II)

(III) $CH{\equiv}C{\cdot}CH_2{\cdot}CH_2{\cdot}CH(CO_2R)_2$ $CH_3{\cdot}C{\equiv}C{\cdot}CH_2{\cdot}CH(CO_2R)_2$ (IV)

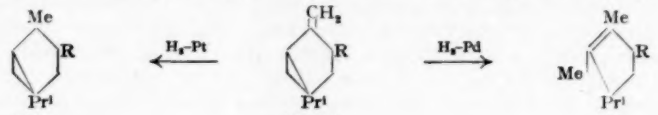
$CH_2{:}C{:}CH{\cdot}CH_2{\cdot}CH(CO_2R)_2$ (V)

(VI) $CH_2{:}CH{\cdot}CH\overset{a}{\text{—}}C(CO_2R)_2$ (bridge CH_2) $CMeR{:}CH{\cdot}CH\text{—}CH{\cdot}CO_2H$ (VII) (bridge CMe_2)

These facts suggested a straight-chain structure with a terminal malonate group and two elements of unsaturation, for example a diene, acetylene, or allene arrangement. There was no high-intensity absorption of ultra-violet light at wave-lengths above 2100 Å. This excluded the conjugated diene structures (I and II; R = H and Et). Ozonolysis of the diacid or its ester, followed by reductive fission of the ozonide, gave formaldehyde, which showed the presence of a terminal double bond and eliminated the acetylenic structures (III) and (IV). At this stage it seemed probable that the diester was identical with the known allene (V; R = Et) (Carothers and Berchet, U.S.P. 2,073,363). However, ozonolysis of our diacid, followed by oxidative fission of the ozonide, gave, not ethane-1 : 1 : 2-tricarboxylic acid, but a tricarboxylic acid, $C_6H_6O_6$. It was saturated to the usual reagents but lacked two hydrogen atoms for a tricarboxy-paraffin. Only *cyclo*propane-1 : 1 : 2-tricarboxylic acid could meet these requirements and our compound was, in fact, identified with this acid by direct comparison. The parent diacid must therefore be 2-vinyl*cyclo*propane-1 : 1-dicarboxylic acid (VI; R = H).

This means that the results of catalytic hydrogenation were misleading in that a reductive fission of the ring had occurred. Incidentally it is noteworthy that the only products isolated (in up to 90% yield) are those with a straight chain corresponding with a fission of bond (*a*) in formula (VI). The catalytic hydrogenation of *cyclo*propane compounds to acyclic products is, of course, well known but usually requires more drastic conditions than are needed for the hydrogenation of double bonds (for references see Shortridge, Craig, Greenlee, Derfer, and Boord, *J. Amer. Chem. Soc.*, 1948, **70**, 946; Simonsen, "The Terpenes," Vol. II, London, 1949). The present examples are, however, noteworthy both for the ease with which they occur, and for the homogeneity of the product. Experiment showed that neither ethyl *cyclo*propane-1 : 1-dicarboxylate nor *cyclo*propane-1 : 1 : 2-tricarboxylic acid was reduced under the conditions used for the hydrogenation of (VI; R = H and Et). *trans*-Chrysanthemum-monocarboxylic acid (VII; R = Me), which is structurally close to (VI; R = H), is reported to give only a dihydro-derivative on catalytic reduction by the Paal–Skita method, the ring remaining intact (Staudinger and Ruzicka, *Helv. Chim. Acta*, 1924, **7**, 201). *trans*-Chrysanthemumdicarboxylic acid (VII; R = CO_2H) is not reduced at all under the same conditions (*idem, loc. cit.*) The behaviour of terpenes containing *cyclo*propane rings is similarly irregular. Thus, reduction of sabinene (VIII; R = H) and of α- and β-thujene with a platinum catalyst gives thujane (IX; R = H) (Tschugaev and Fomin, *Compt. rend.*, 1910, **151**, 1058; Richter, Wolff, and Presting, *Ber.*, 1931, **64**, 876). Similarly sabinol (VIII; R = OH) yields thujyl alcohols (IX; R = OH) (Short and Read, *J.*, 1939, 1040). However, with a palladium catalyst, ring fission occurs in sabinene (Richter *et al.*) and in sabinyl acetate (VIII; R = OAc) (Short and Read), the initial products being olefins to which the structures (X; R = H) and (X; R = OAc)

have been assigned. Unfortunately no experiments have been made on the reduction of Δ^a-carene or norcaradienecarboxylic acid. Hydrogenation of vinyl*cyclo*propane (XI) over Raney nickel gives a mixture of ethyl*cyclo*propane and *n*-pentane (Van Volkenburgh, Greenlee, Derfer, and Boord, *J. Amer. Chem. Soc.*, 1949, **71**, 3595). Recently, reduction of



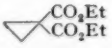
(IX) (VIII) (X)

unsaturated monocyclic *cyclo*propane hydrocarbons without ring fission has been achieved by using a barium-promoted copper chromite catalyst (Slabey and Wise, Natl. Advisory Comm. Aeronautics, Tech. Note 2258—9 (1951); *Chem. Abs.*, 1951, **45**, 7531).

These results seem capable of rationalisation by postulating that when the rings of alkenyl*cyclo*propanes are easily broken, as in the present investigation, the first stage is analogous to the 1 : 4-addition of hydrogen to conjugated dienes (cf. Short and Read, Van Volkenburgh *et al.*, *locc. cit.*). Attempts to effect partial reduction of (VI; R = H) to crotylmalonic acid or to 2-ethyl*cyclo*propane-1 : 1-dicarboxylic acid, by using a palladium on barium sulphate catalyst, met with little success. Although the rate of hydrogenation fell sharply after *ca.* 1·1 mols. of hydrogen had been absorbed, interruption of the reaction at this point gave an unsaturated product which was shown by paper chromatography to contain at least two constituents. One of these was identified, by its R_F value, as *n*-butylmalonic acid.

The ability of a *cyclo*propane ring to conjugate with various chromophores is clearly shown by physical evidence (for references, see Smith and Rogier, *J. Amer. Chem. Soc.*, 1951, **73**, 3840; Mariella and Raube, *ibid.*, 1952, **74**, 518) and by the reductive fission of vinyl*cyclo*propanes referred to above. The electronic interaction with other chromophores which this entails is due to the fact that the electrons in the C–C bonds of *cyclo*propane rings are more weakly bound than the usual σ electrons, and exhibit characteristics usually associated with unlocalised π electrons. Conjugation in (VI; R = Et), involving the three-membered ring, is clearly indicated by an exaltation in molecular refractivity. A comparison (see table) of the observed and calculated refractivities for (VI; R = Et) with those for ethyl *cyclo*propane-1 : 1-dicarboxylate and vinyl*cyclo*propane reveals that the exaltation of our new compound must be due almost exclusively to interaction of the *cyclo*propane ring with the adjacent vinyl group. [The accepted value for the contribution of a *cyclo*propane ring to molecular refractivity (Jeffery and Vogel, *J.*, 1948, 1804) involves the assumption that there is no significant conjugation between a three-carbon ring and a carbalkoxy-group.]

Molecular refractivities.

	R_D (obs.)	R_D (calc.)	Exaltation
	45·60 [1]	45·54 *	0·06
(XI)	23·85 [2]	23·37 *	0·48
	54·96	54·36 *	0·60
		54·41 †	0·55
		54·84 ‡	0·12

* Calculated from the values given by Vogel for CH_2, C, H (*J.*, 1946, 133) and $-CO_2^-$ (*J.*, 1948, 624), and by Jeffery and Vogel for a double bond (*ibid.*, p. 658) and a three-carbon ring (*ibid.*, p. 1804).
† Calculated from the R_D (obs.) for ethyl *cyclo*propane-1 : 1-dicarboxylate.
‡ Calculated from the R_D (obs.) for vinyl*cyclo*propane.
[1] Jeffery and Vogel (*J.*, 1948, 1804).
[2] Calculated from the experimental data of Van Volkenburgh, Greenlee, Derfer, and Boord, *J. Amer. Chem. Soc.*, 1949, **71**, 3595.

Additional evidence for the *cyclo*propane structure of the diester (VI; R = Et) is provided by its infra-red spectrum which exhibits a maximum at 9·8 μ. This coincides with the region (9·8—10 μ) in which alkyl- and alkenyl-substituted *cyclo*propane derivatives

show a strong band, believed to be characteristic of the three-carbon ring (Derfer, Pickett, and Boord, *J. Amer. Chem. Soc.*, 1949, **71**, 2482; Van Volkenburgh, Greenlee, Derfer, and Boord, *loc. cit.*; Slabey and Wise, *loc. cit.*).

The similarity in structure between the product of the malonate reaction and chrysanthemum-monocarboxylic acid (VII; R = Me) suggested that the method developed with conspicuous success for the synthesis of the latter (Campbell and Harper, *J.*, 1945, 283) might also serve as an alternative route to (VI; R = H). Accordingly ethyl diazomalonate was heated with butadiene. From the mixture of products a small amount of a diester was isolated which, on hydrolysis, gave the diacid (VI; R = H) in 2% overall yield, identical with that prepared from dibromobutene.

In addition to (VI; R = Et) the original reaction between dibromobutene and sodiomalonate gave about 20% of an approximately 1 : 3-mixture of the tetracarboxylic esters (XII) and (XIII). The presence of (XIII) in the mixture was established by its conversion, on treatment with sodium ethoxide, into the known ethyl 2-keto-4-vinyl*cyclo*pentane-1 : 3-dicarboxylate (XIV) (following paper) which, as a β-keto-ester, was soluble in alkali and therefore readily isolated. The non-enolic portion of the reaction product consisted of the straight-chain tetra-ester (XII). By hydrogenation, hydrolysis, and decarboxylation it was converted into suberic acid.

$(EtO_2C)_2{\cdot}CH{\cdot}CH_2{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH(CO_2Et)_2$ (XII)

$CH_2{:}CH{\cdot}CH(CH_2{\cdot}CH(CO_2Et)_2){\cdot}CH(CO_2Et)_2$ (XIII)

$CH_2{:}CH{\cdot}CH(CH_2{\cdot}CH(CO_2Et){\cdot}CO){\cdot}CO_2Et$ (XIV)

Concerning the mechanism of the reaction of 1 : 4-dibromobut-2-ene with sodiomalonate a number of points deserve comment. The absence of by-products due to solvolysis suggests that substitution of the bromine atoms does not occur by unimolecular mechanisms involving carbonium ions. For the same reason a migration of the bromine atoms from an α- to a γ-carbon atom before replacement is considered unlikely [cf. ethanolysis of α- and γ-methylallyl bromide in neutral anhydrous alcoholic solution (Catchpole and Hughes, *J.*, 1948, 4)]. Since, however, 1 : 4-dibromobut-2-ene is known to isomerise to 3 : 4-dibromobut-1-ene when heated in the absence of solvent (Farmer, Lawrence, and Thorpe, *J.*, 1928, 729), the 3 : 4-dibromo-compound was substituted for the 1 : 4-isomer in the malonate reaction; no (VI; R = Et) was obtained. It is therefore suggested that replacement of both bromine atoms of 1 : 4-dibromobut-2-ene proceeds, without initial rearrangement, by a bimolecular nucleophilic attack, and that in this respect the reaction conforms to the malonate condensations of other allylic halides.

The substitution of the first bromine atom almost certainly leads to the intermediate (XV), which then reacts further by inter- and intra-molecular processes, mainly the latter. Thus the production of (VI; R = Et) is attributed to substitution of the second bromine atom, probably after formation of the sodio-derivative (XVI), by an intramolecular γ-attack. On an ionic mechanism this may be represented as:

(XV) $BrCH_2{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CH(CO_2Et)_2 \longrightarrow$

$Na^+ \left[Br{-}CH_2{-}CH{=}CH{-}C(COEt)_2 \right] \longrightarrow$ (VI; R = Et)

(XVI)

Soc. chim., 1951, **18**, C43; Catchpole, Hughes, and Ingold, *J.*, 1948, 8; Braude, *Quart. Reviews*, 1950, **4**, 404).

With the intermolecular substitution of (XV) by sodiomalonate there is no obvious reason why bimolecular α-attack, leading to (XII), should not predominate. The formation from dibromobutene of (XIII), in approximately three times the amount of (XII), cannot therefore be satisfactorily attributed to an intermolecular γ-attack of (XV). A more likely explanation is that (XIII) and, to some extent (XII), arise by further reaction of the *cyclo*propane derivative (VI; R = Et) with sodiomalonate [cf. preparation of ethyl butane-1 : 1 : 4 : 4-tetracarboxylate from ethyl *cyclo*propane-1 : 1-dicarboxylate (Bone and Perkin, *J.*, 1895, **67**, 108)]. Evidence in support of this view is advanced in the following paper.

Experimental

The alcohol used as solvent in all malonate condensations was dried by distillation from magnesium ethoxide and finally from a mixture of sodium ethoxide and diethyl phthalate.

Light-absorption data were determined in alcohol.

Condensation of 1 : 4-*Dibromobut-2-ene with Ethyl Sodiomalonate.*—A warm solution of 1 : 4-dibromobut-2-ene (53·5 g.) in alcohol (150 c.c.) was added during 1 hour to a well-stirred solution of sodiomalonate (from 11·5 g. of sodium and 82·5 g. of ethyl malonate) in alcohol (170 c.c.). The mixture was heated under reflux overnight and then cooled and filtered. The filtrate was evaporated under reduced pressure and the residue poured into water. Isolation of the product with ether and distillation gave : (i) *Ethyl* 2-*vinyl*cyclo*propane*-1 : 1-*dicarboxylate* (29·8 g.), b. p. 69—72°/0·5 mm., n_D^{19} 1·4528, n_D^{25} 1·4502, d_4^{25} 1·0381 (Found : C, 62·1; H, 7·45. $C_{11}H_{16}O_4$ requires C, 62·25; H, 7·6%); hydrogenation number : 114, equivalent to 1·85 double bonds. (ii) A mixture (16—20 g.) of ethyl hex-3-ene-1 : 1 : 6 : 6-tetracarboxylate and ethyl 2-vinylbutane-1 : 1 : 4 : 4-tetracarboxylate, b. p. 120° (bath temp.)/10^{-3} mm., n_D^{20} 1·4512 (Found : C, 58·4; H, 7·6. Calc. for $C_{18}H_{28}O_8$: C, 58·05; H, 7·6%); hydrogenation number : 387, equivalent to 0·95 double bonds.

When the condensation was carried out entirely at room temperature the yield of the *cyclo*propane derivative was unaltered but that of the mixture of tetraesters was halved. This mixture, however, showed no appreciable change in composition, determined as described below.

None of the *cyclo*propane derivative was obtained by substitution of either ethyl magnesiomalonate for the sodio-derivative or of 3 : 4-dibromobut-1-ene (Prévost, *Ann. Chim.*, 1928, **10**, 413) for the 1 : 4-dibromo-compound in the above reaction.

Investigation of the low-boiling product

Hydrogenation of (VI; R = Et).—*Ethyl* n-*butylmalonate.* A solution of ethyl 2-vinyl-*cyclo*propane-1 : 1-dicarboxylate (2·6 g.) in methanol (25 c.c.) was shaken in hydrogen in the presence of Adams's catalyst until absorption was complete (hydrogen absorbed equivalent to 1·9 double bonds). Removal of the catalyst and solvent gave ethyl *n*-butylmalonate. This was hydrolysed by heating it under reflux for 1·5 hours with a solution of potassium hydroxide (2·6 g.) in water (2·6 c.c.). Acidification of the aqueous solution and isolation of the product in the usual way gave a solid (1·39 g., 71%), m. p. 96—100°. One recrystallisation from benzene gave *n*-butylmalonic acid (0·97 g.), m. p. 98·5—100·5° undepressed on admixture with an authentic specimen (Hell and Lumpp, *Ber.*, 1884, **17**, 2218, give m. p. 101·5°).

Ozonolysis of (VI; R = Et).—A slow stream of ozonised oxygen (*ca.* 3% of ozone) was bubbled through a cooled solution of ethyl 2-vinyl*cyclo*propane-1 : 1-dicarboxylate (1·0 g.) in glacial acetic acid (AnalaR; 12 c.c.) for 1·5 hours. Zinc dust (1 g.) was added and the mixture was steam-distilled in an atmosphere of nitrogen. The distillate was treated with an excess of dimedone reagent and yielded a solid (0·66 g., 48%), m. p. 185—188°. Recrystallisation of this from aqueous methanol gave the formaldehyde derivative (0·55 g.), m. p. 189° undepressed on admixture with an authentic specimen, m. p. 189°.

2-*Vinyl*cyclo*propane*-1 : 1-*dicarboxylic Acid* (VI; R = H).—Ethyl 2-vinyl*cyclo*propane-1 : 1-dicarboxylate (15·0 g.) was shaken overnight with a solution of potassium hydroxide (15 g.) in water (15 c.c.). The resulting homogeneous solution was extracted thoroughly with ether, and the aqueous layer was then acidified with the calculated amount of cold hydrochloric acid (1 : 1). The solution was thoroughly extracted with ether, and the extract dried (Na_2SO_4) and evaporated. The viscous residue rapidly solidified when scratched. Recrystallisation

from benzene gave the *diacid* (8·4 g.), m. p. 107—108° (Found: C, 53·9; H, 5·4. $C_7H_8O_4$ requires C, 53·8; H, 5·2%).

Hydrogenation of (VI; R = H).—n-*Butylmalonic acid*. A solution of the preceding diacid (1·56 g.) in ethyl acetate (20 c.c.) was shaken in hydrogen in the presence of Adams's catalyst until absorption was complete (497 c.c. of hydrogen were absorbed at 16°/765 mm., equivalent to 2·1 double bonds). Removal of catalyst and solvent gave a solid, m. p. 96—100°. One crystallisation from benzene gave *n*-butylmalonic acid (1·43 g.), m. p. 98·5—101° undepressed on admixture with an authentic specimen.

Reduction of (VI; R = H) in the presence of a 10% palladium on calcium carbonate catalyst similarly gave *n*-butylmalonic acid in 70% yield.

Ozonolysis of (VI; R = H).—(i) Ozonolysis of the diacid and decomposition of the ozonide in the manner described above for the corresponding ethyl ester gave formaldehyde in 38% yield (as the dimedone derivative).

After a solution of (VI; R = H) in glacial acetic acid had been kept for 8 hours and the solvent evaporated under reduced pressure, the diacid was recovered unchanged.

(ii) cyclo*Propane*-1 : 1 : 2-*tricarboxylic acid*. A stream of ozonised oxygen (*ca.* 3% of ozone) was slowly bubbled through a cooled solution of 2-vinyl*cyclo*propane-1 : 1-dicarboxylic acid (2·0 g.) in glacial acetic acid (AnalaR; 25 c.c.) for 10 hours. Hydrogen peroxide (40 c.c.; 20-vol.) was then added and the mixture kept at 20° overnight. The solvents were removed under reduced pressure giving an oil which solidified when scratched. The crude solid had m. p. 182—183° (decomp.) (0·99 g.). One recrystallisation from ether gave *cyclo*propane-1 : 1 : 2-tricarboxylic acid, m. p. 183° (decomp.) undepressed on admixture with an authentic specimen, m. p. 183° (decomp.), prepared from αβ-dibromopropionic acid (for which the authors are indebted to Dr. L. N. Owen) according to Wasserman (*Helv. Chim. Acta*, 1930, **13**, 229; cf. Conrad and Gutzeit, *Ber.*, 1884, **17**, 1185) (Found: C, 41·4; H, 3·6. Calc. for $C_6H_6O_6$: C, 41·4; H, 3·5%).

Condensation of Ethyl Diazomalonate with Butadiene (cf. Staudinger, Muntwyler, Ruzicka, and Seibt, *Helv. Chim. Acta*, 1924, **7**, 391; Campbell and Harper, *J.*, 1945, 283).—Ethyl *iso*-nitrosomalonate was prepared by Redeman and Dunn's method (*J. Biol. Chem.*, 1939, **130**, 344) and hydrogenated at 55°/100 atmospheres, in the presence of a Raney nickel catalyst, to ethyl aminomalonate (77%), b. p. 83—88°/0·3 mm., n_D^{22} 1·4330 (cf. Levene and Schornmuller, *ibid.*, 1934, **106**, 601). This was treated in ethereal solution with hydrogen chloride, and the resulting hydrochloride converted into ethyl diazomalonate by the method of Lindemann, Wolter, and Groger (*Ber.*, 1930, **63**, 702).

A mixture of ethyl diazomalonate (5·0 g.) and butadiene (13 c.c.) was heated at 100° for 22 hours in a stainless-steel autoclave. The resulting mixture, consisting largely of viscous polymers, was then cooled and distilled. The fraction (0·89 g.), b. p. 65—69°/0·5 mm., was shaken overnight with a solution of potassium hydroxide (1·0 g.) in water (1 c.c.). Isolation of the acidic product in the usual way gave an oily solid. Crystallisation from benzene (charcoal) yielded 2-vinyl*cyclo*propane-1 : 1-dicarboxylic acid (90 mg.), m. p. 106—107° undepressed on admixture with the specimen described above. For further identification the diacid was reduced, by using Adams's catalyst, in the manner described above. Two mols. of hydrogen were absorbed giving *n*-butylmalonic acid, m. p. 100° undepressed on admixture with an authentic specimen.

The yield of (VI; R = H) was not improved by carrying out the condensation in the presence of copper bronze.

Investigation of the high-boiling product

A solution of the mixture of tetraesters (11·36 g.) and sodium ethoxide (from 0·625 g. of sodium) in alcohol (60 c.c.) was heated under reflux for 13 hours. The solution was then cooled, diluted with water, and neutralised by the addition of the calculated quantity of dilute (10% w/v) sulphuric acid. The product was extracted with ether, the ethereal extract was washed three times with aqueous potassium hydroxide (2% w/v), and the alkaline aqueous washings were acidified with excess of dilute sulphuric acid (10% w/v). The oil thus precipitated was isolated with ether in the usual way giving an enolic product (5·32 g.), b. p. 110°/0·5 mm., n_D^{18} 1·4663. This was identified as ethyl 2-keto-4-vinyl*cyclo*pentane-1 : 3-dicarboxylate by conversion into 3-ethyl*cyclo*pentanone (71% overall yield) in the manner described in the following paper. The 2 : 4-dinitrophenylhydrazone, formed in 83% yield, crystallised from alcohol in plates, m. p. 77—78° undepressed on admixture with the specimen described in the following paper.

The ethereal solution, after extraction of the enolic material with alkali, was washed with

water, dried, and evaporated giving an oil (2·8 g.), b. p. 120° (bath temp.)/10^{-4} mm. A portion (1·0 g.) in alcohol (10 c.c.) was shaken in hydrogen in the presence of Adams's catalyst until absorption was complete. The catalyst and solvent were removed, and the residue was hydrolysed with aqueous potassium hydroxide. Acidification of the aqueous solution and isolation (continuous ether extraction for 12 hours) of the product led to a crude solid (0·67 g.). This was heated at 170° until the evolution of carbon dioxide ceased. The residue (377 mg.) was crystallised from ethyl acetate (charcoal) and gave suberic acid (131 mg., 28% overall yield), m. p. 139—141° undepressed on admixture with an authentic specimen, m. p. 141°.

The investigations described in this and the following paper were performed during the tenure by one of us (R. W. K.) of a Beaverbrook Overseas Scholarship.

Analyses and light-absorption measurements were carried out in the microanalytical (Mr. F. H. Oliver) and spectrographic (Mrs. A. I. Boston) laboratories of this Department.

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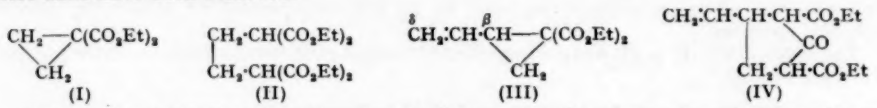
691. cyclo*Propanes. Part II.* The Addition of Ethyl Sodiomalonate to Ethyl* cyclo*Propane*-1 : 1-*dicarboxylate and its* 2-*Vinyl Derivative.*

By R. W. KIERSTEAD, R. P. LINSTEAD, and B. C. L. WEEDON.

Addition of ethyl sodiomalonate to ethyl 2-vinyl*cyclo*propane-1 : 1-dicarboxylate (III) gives the tetraesters (IX) and (X). The former, under the conditions of the reaction, is largely cyclised to ethyl 2-keto-4-vinyl*cyclo*pentane-1 : 3-dicarboxylate (IV). The formation of (X) provides chemical evidence for conjugation between a double bond and a *cyclo*propane ring.

In the preparation of the tetraester (II) from ethyl *cyclo*propane-1 : 1-dicarboxylate (I), by Bone and Perkin's method (*J.*, 1895, **67**, 108), partial cyclisation of the product occurs to give ethyl 2-keto*cyclo*pentane-1 : 3-dicarboxylate (VIII).

THE classical work of Bone and Perkin (*J.*, 1895, **67**, 108) showed that ethyl *cyclo*propane-1 : 1-dicarboxylate (I) reacts with ethyl sodiomalonate to give ethyl butane-1 : 1 : 4 : 4-tetracarboxylate (II), the structure of the product being rigidly proved by acid hydrolysis and decarboxylation to adipic acid. The present communication records an extension of this reaction to the readily available vinyl derivative (III) (cf. Part I; preceding paper). The investigation was undertaken with two main objectives. First, to furnish further chemical evidence for conjugation between a *cyclo*propane ring and a double bond (cf. Part I). Secondly, to throw light on the mechanism of the malonate condensation with 1 : 4-dibromobut-2-ene described in the preceding paper. As will appear in the sequel, both these aims have been achieved.



The reaction of (III) with sodiomalonate did not give the expected good yields of tetraesters. The main product (60%) was found by analysis to be formed by condensation of ethyl malonate and (III), in equimolar proportions, with elimination of the elements of ethyl carbonate. It was shown to contain a readily enolisable ketone group by its solubility in alkali, the formation of a strong colour with ferric chloride, and the preparation of a copper enolate. The presence of a terminal double bond was established by ozonolysis to give formaldehyde, which was isolated as the dimedone derivative in 26% yield. On catalytic reduction it rapidly absorbed one mol. of hydrogen to give a dihydro-derivative which on further hydrogenation was slowly converted into a non-enolic tetrahydro-derivative. Solutions in dilute alkali of the initial product, its dihydro-derivative, and 2-keto-*cyclo*pentane-1 : 3-dicarboxylate (VIII) exhibited very similar light-absorption properties

* Part I, preceding paper.

(see Table 1), indicating that the double bond in the initial material was not conjugated with the enol system.

On the basis of the foregoing evidence the product of the malonate reaction was formulated as (IV). In order to confirm this structure the dihydro-derivative was subjected to acid hydrolysis and decarboxylation. A C_7 ketone was obtained (64%) which yielded a semicarbazone and a di-*m*-nitrobenzylidene derivative, showing the presence of the $-CH_2{\cdot}CO{\cdot}CH_2-$ grouping. Surprisingly neither derivative had a melting point which agreed with those previously reported for the derivatives of 3-ethyl*cyclo*pentanone by von Braun, Kamp, and Kopp (*Ber.*, 1937, **70**, 1754). Although the method employed by the latter authors for the synthesis of their ketone was not free from ambiguity, these discrepancies made it necessary to confirm carefully the correctness of the constitution of (IV), and of the C_7 ketone. The latter had a molecular refractivity (32·50) very close to that calculated (32·62 †) for ethyl*cyclo*pentanone. Further strong support for the five-membered ring was provided by the ultra-violet absorption of the di-*m*-nitrobenzylidene derivative. This was identical with that of the derivative of *cyclo*pentanone but differed appreciably from that of the derivative of *cyclo*hexanone (see Table 2). Conclusive proof

TABLE 1. *Light absorption of keto-esters in alkali.*

	$\lambda_{max.}$, Å	$\varepsilon_{max.}$	Solvent
(IV)	2900	17,500	2% aqueous KOH
	2830 *	16,500	
Dihydro-derivative of (IV)	2910	15,000	"
(VIII)	2900	14,000	"
	2820 *	13,000	
$CH_3{\cdot}CO{\cdot}CH_2{\cdot}CO_2Et$ [1]	2717	30,000	N/10-NaOH

* Inflexion. [1] Grossmann, *Z. phys. Chem.*, 1924, **109**, 330.

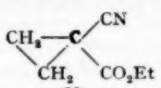
TABLE 2. *Light absorption of di*-m-*nitrobenzylidene derivatives.**

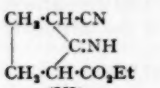
Ketone	$\lambda_{max.}$, Å	$\varepsilon_{max.}$	Ketone	$\lambda_{max.}$, Å	$\varepsilon_{max.}$
3-Ethyl*cyclo*pentanone	2660	16,500	*cyclo*Hexanone	2780	22,000
	2800	16,500		2950	
	3380	43,000		3040	
				3150	
*cyclo*Pentanone	2680	18,000			
	2800	18,000			
	3380	42,000			

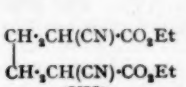
* In chloroform.

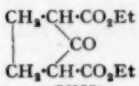
of the structure of the C_7 ketone as 3-ethyl*cyclo*pentanone was provided by nitric acid oxidation which gave a mixture of products from which succinic and β-ethylglutaric acids were isolated.

There is therefore no doubt that our reaction involves the conversion of a three- into a five-membered ring. A very similar process was observed by Best and Thorpe (*J.*, 1909, 685), who found that ethyl 1-cyano*cyclo*propane-1-carboxylate (V) and ethyl cyanoacetate, in the presence of small amounts of the sodio-derivative of the latter, condense to give the imino-compound (VI) in yields of up to 75%. The initial product was shown to be (VII) which was cyclised under the conditions of the reaction.


(V)


(VI)


(VII)


(VIII)

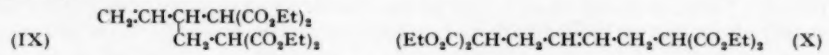
Our results and those of Best and Thorpe differ from those of Bone and Perkin (*loc. cit.*) for the addition of ethyl sodiomalonate to (I). We have accordingly repeated Bone and Perkin's experiment. From the reaction mixture ethyl 2-keto*cyclo*pentane-1 : 3-dicarboxylate (VIII) was isolated in 28% yield. By analogy with the cyanoacetate series, the formation of (VIII) can be ascribed to partial cyclisation of the tetraester (II) first produced. Direct experiment showed that the tetraester (II) cyclises readily to (VIII) in

† Calculated by adding the value for CH_2 (Vogel, *J.*, 1946, 133) to the experimental value for 3-methyl-*cyclo*pentanone (*idem*, *J.*, 1938, 1323).

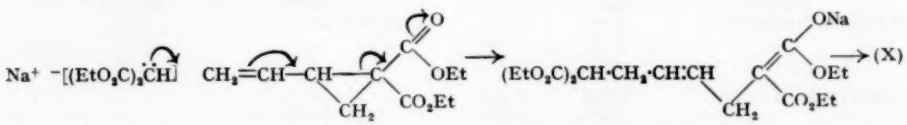
the presence of sodium ethoxide, a fact previously noted by several other authors (Nandi, *J. Indian Chem. Soc.*, 1934, **11**, 277; Meincke, Cox, and McElvain, *J. Amer. Chem. Soc.*, 1935, **57**, 1133; Guha and Seshadriengar, *Ber.*, 1936, **69**, *B*, 1212).

Alkylation of the sodio-derivative of (VIII) with methyl iodide gave (57%) ethyl 2-keto-1 : 3-dimethyl*cyclo*pentane-1 : 3-dicarboxylate. Hydrolysis of this product and decarboxylation led to 2 : 5-dimethyl*cyclo*pentanone.

Returning to the reaction of ethyl sodiomalonate with (III): this also yielded small amounts (12%) of a high-boiling fraction, very similar in composition to the mixture of tetraesters, (IX) and (X), formed as by-product in the condensation of ethyl sodiomalonate with 1: 4-dibromobut-2-ene (Part I). Treatment of the mixture with sodium ethoxide caused cyclisation of the tetraester (IX) to (IV), which was removed by extraction with alkali and shown to be identical with the specimen described above. The residual tetraester was identified by conversion into suberic acid on hydrogenation, hydrolysis, and decarboxylation.



The present investigation has thus shown that addition of sodiomalonate to (III) occurs mainly by attack at $C_{(\beta)}$ to give the branched-chain tetraester (IX), which subsequently undergoes extensive cyclisation to (IV). Simultaneously, however, some attack at $C_{(\delta)}$ takes place with formation of (X). This latter mode of reaction provides chemical confirmation for the existence, previously inferred from molceular-refractivity data (Part I), of electronic interaction between the double bond and the three-carbon ring in (III). The formation of (X) from (III) is analogous to the $\alpha\delta$-addition of sodiomalonate to methyl sorbate and buta-1 : 3-diene-1-carboxylate (Kohler and Butler, *J. Amer. Chem. Soc.*, 1926, **48**, 1036; Farmer and Healey, *J.*, 1927, 1060; Farmer and Mehta, *J.*, 1930, 1610) and the following mechanism is proposed :



In the preceding paper it was suggested that the branched-chain tetraester (IX) and, to some extent, its isomer (X), formed as by-products in the condensation of 1 : 4-dibromobut-2-ene with ethyl sodiomalonate, arise by further reaction of (III) produced initially. While the present findings lend support to this view, the failure of the tetraester (IX) to undergo any appreciable cyclisation in the dibromobutene condensation still requires explanation. In the addition of ethyl sodiomalonate to (III), cyclisation of (IX) will be promoted by the alkoxide formed during the course of the reaction. In the dibromobutene condensation, however, no appreciable concentration of alkoxide is built up and consequently any cyclisation is brought about by the sodiomalonate. Investigation showed that the latter is a poor condensing agent, compared with sodium ethoxide, for the conversion of (IX) into (IV). The experimental conditions in the dibromobutene condensation do not therefore favour cyclisation of the tetraester (IX).

Experimental

Alcohol was dried as outlined in Part I.

*Ethyl 2-Keto-4-vinyl*cyclo*pentane-1 : 3-dicarboxylate* (IV).—Ethyl malonate (8·5 g., 2 mols.) was added to a stirred solution of sodium ethoxide [from sodium (0·61 g., 1 mol.)] in alcohol (60 c.c.), and the mixture was heated under reflux for ½ hour. Ethyl 2-vinyl*cyclo*propane-1 : 1-dicarboxylate (5·64 g.; 1 mol.) was added and heating was continued overnight. The mixture was cooled, diluted with water, acidified with dilute sulphuric acid (10% w/v), and then extracted with ether. The ethereal solution was washed twice with aqueous potassium hydroxide (2% w/v). The ethereal layer was dried and evaporated giving a mixture (1·2 g.) of tetraesters, the examination of which is described later. The alkaline extract was acidified with dilute sulphuric acid, and the oil thus precipitated was isolated with ether in the usual way. Distil-

lation gave *ethyl* 2-*keto*-4-*vinyl*cyclo*pentane*-1 : 3-*dicarboxylate* (3·6 g., 54%), b. p. 120°/0·5 mm., 105°/0·05 mm., n_D^{24} 1·4635 (Found : C, 61·5; H, 7·3. $C_{13}H_{18}O_5$ requires C, 61·4; H, 7·1%) (hydrogenation number, 247; equivalent to 1·0 double bond). It dissolved slowly in aqueous sodium hydroxide (5% w/v) and rapidly in aqueous potassium hydroxide (5% w/v). The *copper* enolate crystallised from alcohol, on the addition of water, in green needles, m. p. 137—138° (decomp.) (Found : C, 54·35; H, 5·95. $C_{26}H_{34}O_{10}Cu$ requires C, 54·75; H, 6·0%).

In another experiment, using equimolar quantities of ethyl malonate and ethyl 2-vinyl-*cyclo*propane-1 : 1-dicarboxylate, the crude product was distilled, without initial separation by extraction with alkali, and gave (IV) in 60% yield. This yield was unaffected by adding the ethyl malonate and the *cyclo*propane derivative simultaneously to the sodium ethoxide solution, instead of preforming the ethyl sodiomalonate.

Ozonolysis of (IV).—A slow stream of ozonised oxygen (*ca.* 3% of ozone) was bubbled through a cooled solution of the preceding diester (1·0 g.) in glacial acetic acid (AnalaR; 12 c.c.) for 4½ hours. Zinc dust (1·0 g.) was then added and the mixture was steam-distilled in an atmosphere of nitrogen. The distillate was treated with an excess of dimedone reagent and yielded the derivative of formaldehyde which crystallised from aqueous methanol in needles (0·295 g., 26%), m. p. and mixed m. p. 188—189·5°.

Ethyl 4-*Ethyl*-2-*keto*cyclo*pentane*-1 : 3-*dicarboxylate*.—A solution of (IV) (6·0 g.) in alcohol (45 c.c.) was shaken in hydrogen in the presence of Adams's catalyst until one mol. of hydrogen had been absorbed (562 c.c. at 17·5°/764 mm.). The rate of absorption had then become very slow, and the reaction was interrupted. Removal of catalyst and solvent and distillation of the residue gave *ethyl* 4-*ethyl*-2-*keto*cyclo*pentane*-1 : 3-*dicarboxylate* (4·4 g.), b. p. 115°/0·09 mm., n_D^{25} 1·4529 (Found : C, 60·7; H, 8·1. $C_{13}H_{20}O_5$ requires C, 60·9; H, 7·85%). It gave a strong violet colour with ferric chloride solution.

Ethyl 4-*Ethyl*-2-*hydroxy*cyclo*pentane*-1 : 3-*dicarboxylate*.—A solution of (IV) (3·0 g.) in alcohol (20 c.c.) was shaken in hydrogen in the presence of Adams's catalyst until absorption was complete (565 c.c. of hydrogen absorbed at 21°/759 mm., equivalent to 2·0 double bonds). Isolation of the product in the usual manner gave the cyclo*pentanol* (2·0 g.), b. p. 115°/0·6 mm., n_D^{21} 1·4567 (Found : C, 60·3; H, 8·4. $C_{13}H_{22}O_5$ requires C, 60·4; H, 8·6%). It was insoluble in alkali and gave no colour with ferric chloride solution.

3-*Ethyl*cyclo*pentanone*.—A mixture of ethyl 4-ethyl-2-keto*cyclo*pentane-1 : 3-dicarboxylate (6·2 g.) and dilute sulphuric acid (50 c.c.; 20% w/v) was heated under reflux for 4 hours. The mixture was then steam-distilled and the product was isolated from the distillate by extraction with ether in the usual way. Distillation gave 3-*ethyl*cyclo*pentanone* (1·73 g.), b. p. 165°, n_D^{25} 1·4355, d_D^{25} 0·9015 (Found : C, 75·1; H, 10·5. $C_7H_{12}O$ requires C, 74·95; H, 10·8%). The 2 : 4-*dinitrophenylhydrazone* crystallised from alcohol in plates, m. p. 78° (Found : C, 53·55; H, 5·6. $C_{13}H_{16}O_4N_4$ requires C, 53·4; H, 5·5%). The *semicarbazone* crystallised from aqueous methanol in plates, m. p. 166° (Found : C, 56·9; H, 9·1. $C_8H_{15}ON_3$ requires C, 56·8; H, 8·9%). The *di*-m-*nitrobenzylidene* derivative crystallised from alcohol–ethyl acetate in prisms, m. p. 156·5° (Found : N, 7·3. $C_{21}H_{18}O_5N_2$ requires N, 7·4%).

For the semicarbazone and the di-*m*-nitrobenzylidene derivative of a ketone stated to be 3-ethyl*cyclo*pentanone, von Braun, Kamp, and Kopp (*Ber.*, 1937, **70**, 1754) give m. p. 175° and 142°, respectively.

The *di*-m-*nitrobenzylidene* derivative of *cyclo*pentanone crystallised from alcohol–ethyl acetate in needles, m. p. 222° (Found : N, 8·25. $C_{19}H_{14}O_5N_2$ requires N, 8·0%). The corresponding derivative of *cyclo*hexanone crystallised from alcohol–ethyl acetate in monoclinic prisms, m. p. 191° (Found : N, 7·6. $C_{20}H_{16}O_5N_2$ requires N, 7·7%).

Oxidation of 3-*Ethyl*cyclo*pentanone*. β-*Ethylglutaric Acid*.—3-Ethyl*cyclo*pentanone (1·5 g.) was added to warm nitric acid (15 c.c.; 40% w/v) at such a rate that the temperature of the mixture was kept at 78—81°. The mixture was then diluted with water, and the resulting solution evaporated on the steam-bath. The residue was triturated with benzene, and the insoluble portion was separated. One crystallisation from ethyl acetate–benzene gave succinic acid (88 mg.), m. p. 183—184° undepressed on admixture with an authentic specimen. Evaporation of the benzene solution gave an acidic oil (1·3 g.), a portion (325 mg.) of which was converted into the *benzylamine* salt (700 mg.). This crystallised from ethyl acetate in plates, m. p. 152° (Found : C, 67·25; H, 7·75. $C_{21}H_{30}O_4N_2$ requires C, 67·35; H, 8·1%). Regeneration of the acid from the salt (188 mg.) in the usual manner gave a solid (84 mg.) which was crystallised twice from benzene–light petroleum (b. p. 40—60°) yielding β-ethylglutaric acid, m. p. 71·5—73° undepressed on admixture with an authentic specimen (Day and Thorpe, *J.*, 1920, **117**, 1470, give m. p. 73°).

Ethyl 2-*Keto*cyclo*pentane*-1 : 3-*dicarboxylate* (VIII).—(i) *From ethyl* cyclo*propane*-1 : 1-*dicarboxylate*. Ethyl *cyclo*propane-1 : 1-dicarboxylate was prepared from ethylene dibromide and ethyl malonate according to Bone and Perkin (*loc. cit.*; cf. Dox and Yoder, *J. Amer. Chem. Soc.*, 1921, **43**, 2097). Distillation of the product through a Stedman column (12″ × 1″) gave a fraction, b. p. 103°/17 mm., n_D^{23} 1·4287 (Found : C, 57·25; H, 7·7%), which was estimated from the analysis and refractive index to contain the required *cyclo*propane derivative and ethyl malonate in the proportion 4 : 1.

A mixture of ethyl *cyclo*propane-1 : 1-dicarboxylate (8·8 g.; 80% pure) and ethyl malonate (6·0 g.) was added to sodium ethoxide (from 1·0 g. of sodium) in alcohol (15 c.c.), and the solution was heated under reflux for 8 hours. The solvent was removed under reduced pressure and the residue was acidified with sulphuric acid (10% w/v). Isolation of the product with ether and distillation yielded ethyl 2-keto*cyclo*pentane-1 : 3-dicarboxylate (2·37 g.), b. p. 93°/0·15 mm., n_D^{20} 1·4556 (Found : C, 57·8; H, 7·2; OEt, 39·7. Calc. for $C_{11}H_{16}O_5$: C, 57·9; H, 7·1; OEt, 39·5%). The copper enolate crystallised from aqueous alcohol in needles, m. p. 187° (decomp.) (Found : C, 51·3; H, 6·1. Calc. for $C_{22}H_{30}O_{10}Cu$: C, 51·0; H, 5·8%) (Guha and Seshadriengar, *Ber.*, 1936, **69**, *B*, 1212, give m. p. 200°). The diester was converted into the dianilide which crystallised from alcohol in needles, m. p. 199—201° (Found : C, 71·1; H, 5·9. Calc. for $C_{19}H_{18}O_2N_2$: C, 70·8; H, 5·6%) (Mitchell and Thorpe, *J.*, 1910, 1003, give m. p. 195°).

A mixture of ethyl 3-keto*cyclo*pentane-1 : 3-decarboxylate (609 mg.) and sulphuric acid (5 c.c.; 25% w/v) was heated under reflux for 2 hours and then steam-distilled. Isolation of the product from the distillate and treatment with excess of Brady's reagent gave *cyclo*pentanone 2 : 4-dinitrophenylhydrazone which crystallised from methanol–ethyl acetate in plates (195 mg.), m. p. and mixed m. p. 144°.

The high-boiling product from the reaction of ethyl *cyclo*propane-1 : 1-dicarboxylate with ethyl sodiomalonate was not investigated.

(ii) *Cyclisation of Ethyl Butane*-1 : 1 : 4 : 4-*tetracarboxylate* (II).—The tetraester (II) (15·0 g.) (Noyes and Kyriakides, *J. Amer. Chem. Soc.*, 1910, **32**, 1057) was added to sodium ethoxide (from 1·0 g. of sodium) in alcohol (100 c.c.), and the solution was heated under reflux for 13 hours. Water was added, the mixture was acidified with dilute sulphuric acid, and the product was isolated with ether. Distillation gave ethyl 2-keto*cyclo*pentane-1 : 3-dicarboxylate (6·3 g., 63%), b. p. 88°/0·1 mm., n_D^{20} 1·4568. The copper enolate had m. p. 189° (decomp.) undepressed on admixture with the specimen described above. The dianilide had m. p. 199—200° undepressed on admixture with the specimen described above.

Ethyl 2-*Keto*-1 : 3-*dimethyl*cyclo*pentane*-1 : 3-*dicarboxylate*.—Ethyl 2-keto*cyclo*pentane-1 : 3-dicarboxylate (4·06 g.) was added to a stirred suspension of sodium ethoxide (from 0·82 g. of sodium) in benzene (15 c.c.). The mixture was heated under reflux for ½ hour and then cooled. Methyl iodide (15·0 g.) was added rapidly to the deep-red solution. After the vigorous reaction had subsided, the resulting suspension was heated under reflux for ½ hour. The suspension was cooled, diluted with water, and extracted with ether. The extract was washed with aqueous potassium hydroxide (2% w/v), dried, and evaporated. Distillation of the residue gave *ethyl* 2-*keto*-1 : 3-*dimethyl*cyclo*pentane*-1 : 3-*dicarboxylate* (2·6 g., 57%), b. p. 85°/0·2 mm., n_D^{20} 1·4478 (Found : C, 60·7; H, 7·65; OEt, 35·0. $C_{13}H_{20}O_5$ requires C, 60·9; H, 7·9; OEt, 35·2%). It gave no colour with ferric chloride.

2 : 5-*Dimethyl*cyclo*pentanone*.—(i) A mixture of the preceding diester (1·2 g.) and sulphuric acid (10 c.c.; 25% w/v) was heated under reflux for 12 hours and then steam-distilled. Saturation of the distillate with ammonium sulphate and isolation of the product in the usual way gave the crude ketone (360 mg.) which possessed a camphor-like odour. It gave, in 86% yield, a mixture of 2 : 4-dinitrophenylhydrazones, m. p. 147—150°, from which, by chromatographic adsorption on alumina from benzene solution and repeated crystallisation from alcohol–ethyl acetate, one geometrical *isomer* was isolated as needles, m. p. 172—172·5° (Found : C, 53·6; H, 5·6. $C_{13}H_{16}O_4N_4$ requires C, 53·4; H, 5·5%). The ketone gave a mixture of semicarbazones in poor yield.

(ii) A mixture of ethyl 2-keto-1 : 3-dimethyl*cyclo*pentane-1 : 3-dicarboxylate (1·12 g.) and aqueous potassium hydroxide (15 c.c.; 10% w/v) was heated under reflux for 4 hours and then steam-distilled. Isolation of the product as above gave the crude ketone (254 mg.). The 2 : 4-dinitrophenylhydrazone crystallised from ethyl acetate in needles, m. p. 172—172·5° undepressed on admixture with the specimen described above. The semicarbazone, after several crystallisations from methanol, was obtained as plates, m. p. 191° (Harper, Kon, and Ruzicka, *J.*, 1934, 34, give m. p. 190—191°).

Examination of the Mixed Tetraesters from the Preparations of (IV).—A portion (1·14 g.) of

the mixture of tetraesters, n_D^{20} 1·4515, was added to sodium ethoxide (from 75 mg. of sodium) in alcohol (10 c.c.), and the solution was heated under reflux overnight. The solution was cooled, diluted with water, acidified with sulphuric acid (10% w/v), and then extracted with ether. The ethereal extract was washed with aqueous potassium hydroxide (2% w/v), dried, and evaporated. Distillation of the residue (253 mg.) gave an oil (163 mg.), b. p. 120°(bath)/10^{-5} mm. Hydrogenation, hydrolysis, and subsequent decarboxylation, in the manner described previously (Part I) for the tetraester from the condensation of 1 : 4-dibromobut-2-ene with sodiomalonate, gave a crude acid. Crystallisation (charcoal) from ethyl acetate yielded suberic acid (6·3 mg.), m. p. 138—140° undepressed on admixture with an authentic specimen.

The above alkaline extract was acidified with dilute sulphuric acid (10% w/v), and the oil thus precipitated was isolated with ether in the usual way. Distillation of the crude product (616 mg.) gave ethyl 2-keto-4-vinyl*cyclo*pentane-1 : 3-dicarboxylate (350 mg.), b. p. 90° (bath temp.)/10^{-4} mm. The copper enolate had m. p. 137·5° (decomp.), undepressed on admixture with the specimen described above.

Analyses and light-absorption measurements were carried out in the microanalytical (Mr. F. H. Oliver) and spectrographic (Mrs. A. I. Boston) laboratories of this Department.

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692. *Anodic Syntheses. Part VI.* Chain Extension of Fatty Acids by an Isoprene Unit.*

By R. P. Linstead, J. C. Lunt, B. C. L. Weedon, and (in part) B. R. Shephard.

The synthesis of (δ)-ethyl (α)-hydrogen γ-methyladipate (I), and the use of this half-ester in symmetrical and unsymmetrical anodic coupling reactions, are described.

A new method for extending the carbon chain of fatty acids by one isoprene unit (·CH_2·CH_2·CHMe·CH_2·) is illustrated by the synthesis of 3-methyldecanoic acid from *n*-hexanoic acid and (I).

An attractive feature of the Kolbe reaction is the convenient synthetical route which it affords to many branched-chain compounds. Anodic coupling occurs readily on electrolysis of alkyl-substituted fatty acids and half-esters, provided that they are unsubstituted in the α-position, to give hydrocarbons and diesters, respectively. A process of still wider application, permitting the synthesis of unsymmetrical molecules, consists in the electrolysis of mixtures of fatty acids and/or half-esters whereby symmetrical coupling is accompanied by " crossed " coupling of the two components (for references see Linstead, Lunt, and Weedon, *J.*, 1950, 3326). It has recently been shown that these methods are also applicable to the preparation, from optically active intermediates, of pure enantiomorphs of several branched-chain diesters and fatty acids (Linstead, Lunt, and Weedon, *J.*, 1950, 3333; 1951, 1130; Ställberg-Stenhagen, *Arkiv Kemi*, 1950, **2**, 95, 431; 1951, **3**, 249, 273; Cavanna and Ställberg-Stenhagen, *Atti R. Accad. Lincei*, 1950, **3**, 31).

In view of the frequent occurrence in nature of compounds with a polyisoprenoid carbon skeleton, it seemed of considerable interest to devise an electrolytic method for extending the carbon chain of a fatty acid, in successive stages, by one isoprene unit at a time :

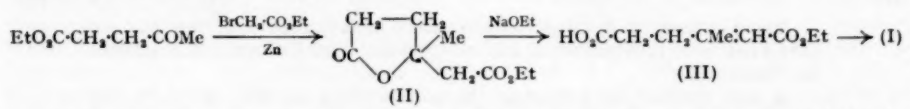
$$R\cdot[CH_2\cdot CH_2\cdot CHMe\cdot CH_2]_n\cdot CO_2H + \underset{(I)}{HO_2C\cdot CH_2\cdot CH_2\cdot CHMe\cdot CH_2\cdot CO_2Et} \xrightarrow[\text{(ii) hydrolysis}]{\text{(i) Kolbe}} R\cdot[CH_2\cdot CH_2\cdot CHMe\cdot CH_2]_{n+1}\cdot CO_2H$$

To this end a synthesis of (δ)-ethyl (α)-hydrogen γ-methyladipate (I) has been developed, and the ability of this half-ester to undergo anodic cross-coupling with a fatty acid demonstrated.

* Part V, *J.*, 1951, 2854.

The problem of preparing the intermediate (I), uncontaminated by the isomeric half-ester, (δ)-ethyl (α)-hydrogen β-methyladipate, was successfully solved in the following manner. Condensation of ethyl lævulate and ethyl bromoacetate in the presence of zinc gave, as described earlier by Staudinger and Ruzicka (*Helv. Chim. Acta*, 1924, **7**, 251; cf. Duden and Freydag, *Ber.*, 1903, **36**, 953), the lactonic ester (II) in 30% yield. This was readily isomerised in 85% yield to the unsaturated half-ester (III) by treatment with sodium ethoxide following the procedure developed previously with related compounds (Pauly and Will, *Annalen*, 1918, **416**, 1; Elvidge, Linstead, Orkin, Sims, Baer, and Pattison, *J.*, 1950, 2228; Elvidge, Linstead, Orkin, and Sims, *J.*, 1950, 2235; Elvidge, Linstead, and Sims, *J.*, 1951, 3386; Elvidge, Linstead, and Smith, *J.*, 1952, 1026). The structure of (III) was confirmed by its light-absorption properties, which were in good agreement with those expected for an αβ-unsaturated ester, by ozonolysis to lævulic acid (isolated as its semicarbazone in 70% yield), and by hydrolysis to the known *trans*-Δ^{α}-dihydro-β-methylmuconic acid (Elvidge, Linstead, and Sims, *loc. cit.*). The required saturated half-ester (I) was obtained in 95% yield on catalytic hydrogenation of (III). Hydrolysis of (I) yielded β-methyladipic acid.

Electrolysis of ethyl hydrogen γ-methyladipate (I) in methanol proceeded normally to give ethyl ββ′-dimethylsebacate (IV) in 70% yield. By carrying out the reaction in the presence of an excess of *n*-hexanoic acid anodic cross-coupling occurred, and, after hydrolysis of the ester formed, 3-methyldecanoic acid (V) was isolated in 65% yield. It readily furnished a tribromoanilide and a *p*-bromophenacyl ester, having melting points in good agreement with those reported previously (Wilson, *J. Amer. Chem. Soc.*, 1945, **67**, 2162). The purity of the final product provides convincing evidence for the homogeneity of the intermediate half-ester (I).



$(CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}CH_2{\cdot}CO_2Et)_2$ (IV) $Me{\cdot}[CH_2]_4{\cdot}CH_2{\cdot}CH_2{\cdot}CHMe{\cdot}CH_2{\cdot}CO_2H$ (V) $(CH_2{\cdot}CH_2{\cdot}CMe{:}CH{\cdot}CO_2Et)_2$ (VI)

Although investigations now in hand on the use of unsaturated components in the Kolbe reaction will be reported in a subsequent paper in this series, it is convenient at the present stage to record that electrolysis in methanol of the unsaturated half-ester (III) gives the diene diester (VI) in 55% yield. Previously Fichter and Holbro (*Helv. Chim. Acta*, 1937, **20**, 333) have shown that unsaturated acids, other than those with a double bond in either the αβ or the βγ position, undergo at least partial coupling at the anode.

Experimental

Light-absorption data were determined in ethanol.

Commercial absolute methanol was used as solvent in the electrolyses without purification.

n-Hexanoic acid was prepared by catalytic hydrogenation of crystalline sorbic acid.

γ-Carbethoxymethyl-γ-methylbutanolide (II) (cf. Staudinger and Ruzicka, *Helv. Chim. Acta*, 1924, **7**, 251).—About one tenth of a solution of ethyl lævulate (100 g., 0·7 mole) and redistilled ethyl bromoacetate (120 g., 0·72 mole) in benzene (100 c.c.) was added to a stirred suspension of activated zinc wool (54 g., 0·83 mole) in benzene (40 c.c.), containing a trace of iodine. The mixture was warmed and when reaction commenced the remainder of the solution of lævulate and bromoacetate was added at such a rate that gentle refluxing was maintained. When the addition was complete, the mixture was heated for a further ½ hour, then cooled and poured into a solution of acetic acid (70 g.) in water (250 c.c.). Isolation of the product by extraction with benzene and distillation gave γ-carbethoxymethyl-γ-methylbutanolide (41 g.), b. p. 113°/0·5 mm., n_D^{21} 1·4520 (Found: C, 58·3; H, 7·6. Calc. for $C_9H_{14}O_4$: C, 58·05; H, 7·6%) (*idem*, *ibid.*, give b. p. 165—170°/15 mm.).

4-Carbethoxy-3-methylbut-3-ene-1-carboxylic Acid (III).—A solution of anhydrous alcoholic sodium ethoxide (65 c.c., 2·06N) was added to a solution of the lactonic ester (25·0 g.) in alcohol (35 c.c.), and the mixture kept at 20° for 20 minutes. Most of the solvent was removed under

reduced pressure, and water (40 c.c.) was then added. After thorough extraction with ether, the aqueous solution was covered with a layer of light petroleum (b. p. 40—60°) and ether (3 : 1; 300 c.c.), and the mixture cooled to 0°. Dilute sulphuric acid (42 c.c., 3·03N; 95% of theoretical) was added gradually with shaking. The aqueous layer was separated and extracted with further quantities (4 × 70 c.c.) of the same solvent mixture. The combined extracts were dried and evaporated. Distillation of the residue gave the *half-ester* (22 g.), b. p. 124—125°/0·5 mm. (Found: C, 58·2; H, 7·7. $C_9H_{14}O_4$ requires C, 58·05; H, 7·6%). Light absorption: maximum, 2160 Å; ε, 13,000. The distillate was collected in several fractions, having n_D^{25} ranging from 1·4683 to 1·4704 and equivalents from 194·1 to 186·6 ($C_9H_{14}O_4$ requires 186·2) indicating a contamination of the total product with *ca.* 2% of the starting lactonic ester. The S-*benzylthiuronium* salt crystallised from alcohol in needles, m. p. 144—145° (Found: C, 58·25; H, 6·9. $C_{17}H_{24}O_4N_2S$ requires C, 57·95; H, 6·85%). The *piperazine* salt was difficult to purify but after six crystallisations from acetone had m. p. 127—128·5° (Found: C, 58·0; H, 8·5. $C_{22}H_{38}O_8N_2$ requires C, 57·6; H, 8·35%).

When the liberation of the half-ester from the aqueous solution of its sodium salt was carried out at room temperature, the percentage of lactonic impurity in the product was increased slightly.

Ozonolysis of 4-*Carbethoxy*-3-*methylbut*-3-*ene*-1-*carboxylic Acid* (III).—Ozonised oxygen was passed for 5 hours (*ca.* 200—300 mg. of ozone/hour) through a cooled (0°) solution of the half-ester (1·5 g.) in acetic acid ("AnalaR"; 15 c.c.). Water (30 c.c.) and hydrogen peroxide (5 c.c.; 90-vol.) were then added and the mixture was steam-distilled to complete the decomposition of the ozonide and remove the acetic acid. The residue was concentrated to a small volume (*ca.* 12 c.c.) and treated with an excess of an aqueous methanolic solution of semicarbazide acetate. This gave a crude derivative (1·0 g., 72%), m. p. 178° (decomp.), which on crystallisation from aqueous (1 : 1) methanol yielded the semicarbazone of lævulic acid as prisms, m. p. 181·5° (decomp.) undepressed on admixture with an authentic specimen, m. p. 182° (decomp.).

trans-Δ^{α}-*Dihydro*-β-*methylmuconic Acid*.—A solution of the half-ester (0·5 g.) in N-potassium hydroxide (8 c.c.) was kept at 20° for 7 hours and then made just acid (Congo-red) with 2N-hydrochloric acid. When kept the solution deposited needles (0·17 g.), m. p. 139—146°. Four recrystallisations from benzene–ethyl acetate (1 : 1) gave the diacid, m. p. 157—160° (m. p. depends on rate of heating). A mixture with a sample, m. p. 158—161°, of the diacid prepared by Elvidge, Linstead, and Sims (*J.*, 1951, 3386) had m. p. 158—161°.

(δ)-*Ethyl* (α)-*Hydrogen* γ-*Methyladipate* (I).—A solution of the unsaturated half-ester (40·8 g.) in ethyl acetate (100 c.c.) was shaken in hydrogen in the presence of Adams's catalyst (250 mg.) until absorption was complete (hydrogen absorbed equivalent to 1·0 double bond). The catalyst was removed and the solution shaken with sodium hydrogen carbonate (24 g.) in water (240 c.c.). The aqueous layer was separated, extracted with ether, and acidified with the calculated amount of 3N-sulphuric acid. Isolation of the precipitated oil with ether and distillation gave (δ)-*ethyl* (α)-*hydrogen* γ-*methyladipate* (37·0 g., 94%), b. p. 133°/1 mm., n_D^{21} 1·4400 (Found: C, 57·6; H, 8·75%; equiv., 188·1. $C_9H_{16}O_4$ requires C, 57·45; H, 8·55%; equiv., 188·2). The S-*benzylthiuronium* salt crystallised from alcohol in plates, m. p. 133° (Found: C, 57·9; H, 7·75. $C_{17}H_{26}O_4N_2S$ requires C, 57·6; H, 7·4%).

β-*Methyladipic Acid*.—A solution of the preceding half-ester (0·5 g.) and potassium hydroxide (0·55 g.) in water (5 c.c.) was heated for 40 minutes on a steam-bath. The solution was then acidified with 2N-hydrochloric acid and extracted thoroughly with ether. The extract was dried and evaporated giving β-methyladipic acid which crystallised from benzene as needles (0·33 g., 78%), m. p. 92·5—93·5° undepressed on admixture with an authentic specimen, m. p. 94°.

Ethyl ββ′-*Dimethylsebacate* (IV).—The saturated half-ester (I) (9·0 g.) was added to a solution of sodium methoxide (from 0·3 g. of sodium) in methanol (40 c.c.). The resulting solution was cooled in an ice-bath and electrolysed in the usual manner, by using two platinum plates (4 × 2·5 cm.) placed *ca.* 1·5 mm. apart as electrodes and a current of 1·6—2·0 amps., until the electrolyte became slightly alkaline (65 minutes). The electrolyte was neutralised by the addition of acetic acid, the methanol was removed under reduced pressure, and the residue was dissolved in ether. The ethereal solution was shaken with sodium hydrogen carbonate solution and dried. Distillation gave the *diester* (4·7 g.), b. p. 127—130° (mainly 127—128°)/0·5 mm., n_D^{25} 1·4360 (Found: C, 67·05; H, 10·7. $C_{16}H_{30}O_4$ requires C, 67·1; H, 10·55%).

3-*Methyldecanoic Acid* (V) (With B. R. Shephard).—A solution of ethyl hydrogen β-methyladipate (7·8 g., 0·04 mole) and *n*-hexanoic acid (31·5 g., 0·27 mole) in methanol (50 c.c.), containing sodium methoxide (from 0·14 g. of sodium), was electrolysed in the manner described

above. The resulting solution was neutralised by the addition of acetic acid, and the solvent was evaporated. The residue was hydrolysed and the product separated into neutral and acidic portions, giving decane (10·3 g.), b. p. 172—174°/760 mm., and 3-methyldecanoic acid (5·1 g.), b. p. 156°/15 mm., n_D^{21} 1·4361 (Found : equiv., 187. Calc. for $C_{11}H_{22}O_2$: equiv., 186). The tribromoanilide, prepared in 75% yield, crystallised from ethanol in needles, m. p. 119·5° (Found : Br, 48·6. Calc. for $C_{17}H_{24}ONBr_3$: Br, 48·1%) (Wilson, *J. Amer. Chem. Soc.*, 1945, **67**, 2162, gives m. p. 117—117·5°; Polgar and Robinson, *J.*, 1945, 389, give m. p. 111·5°). The *p*-bromophenacyl ester, prepared in 65% yield, crystallised from aqueous methanol in needles, m. p. 38·5—39° (Wilson, *loc. cit.*, gives m. p. 39—40°).

Ethyl 2 : 7-*Dimethylocta*-1 : 7-*diene*-1 : 8-*dicarboxylate* (VI).—The unsaturated half-ester (18·8 g., 0·1 mole) was added to a solution of sodium methoxide [from sodium (0·07 g., 0·003 mole)]. The resulting solution was cooled in an ice-bath and electrolysed in the manner described above (150 minutes). Neutralisation of the electrolyte and isolation of the product in the usual way gave the *diester* (7·75 g.), b. p. 130—132°/0·2 mm., n_D^{23} 1·4772 (Found : C, 67·95; H, 9·45. $C_{16}H_{24}O_4$ requires C, 68·05; H, 9·3%) (hydrogen number : 148, equivalent to 1·9 double bonds). Light absorption : maximum, 2180 Å; ε, 28,500.

When the electrolysis was carried out in ethanolic solution the electrodes became covered with a polymeric material and the current dropped rapidly to zero.

One of us (J. C. L.) thanks the Department of Scientific and Industrial Research for a Maintenance Grant and another (B. R. S.) the London County Council for a Grant.

Analyses and light-absorption measurements were carried out in the microanalytical (Mr. F. H. Oliver) and spectrographic (Mrs. A. I. Boston) laboratories of this Department.

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693. *Anodic Syntheses. Part VII.* Electrolyses of Mono-, Di-, and Tri-phenylacetic Acids in Non-aqueous Solutions.*

By R. P. Linstead, B. R. Shephard, and B. C. L. Weedon.

The work of previous authors on the electrolyses of mono-, di-, and tri-phenylacetic acids in non-aqueous solutions has been extended.

Phenyl-substitution of acetic acid hinders the normal Kolbe coupling reaction and favours anodic methoxylation and acetoxylation in methanol and acetic acid, respectively.

As part of an exploratory investigation of the anodic reactions of substituted fatty acids (see Part V, Linstead, Shephard, and Weedon, *J.*, 1951, 2854) the electrolysis of mono-, di-, and tri-phenylacetic acids in non-aqueous solvents has been studied.

Previous work on this subject has been largely confined to experiments carried out in a mixture of methanol and pyridine, the latter being added to limit the deposition of polymeric materials which otherwise tend to coat the anode. In this mixture of solvents electrolysis of monophenylacetic acid gives dibenzyl in 50% yield by the normal Kolbe coupling reaction (Fichter and Stenzl, *Helv. Chim. Acta*, 1939, **22**, 976). Very similar yields have now been obtained by using methanol alone as solvent, and by electrolysing fused phenylacetic acid without added solvent.

With diphenylacetic acid the Kolbe reaction is largely suppressed, the main product (35%) in methanol–pyridine being diphenylmethyl methyl ether (van der Hoek and Nauta, *Rec. Trav. chim.*, 1942, **61**, 845). Under similar conditions triphenylacetic acid is reported to give (18%) triphenylmethyl peroxide (Riccoboni, *Gazzetta*, 1940, **70**, 748). In our hands the electrolysis of triphenylacetic acid in methanol alone has led to the formation of methyl triphenylmethyl ether, in 60% yield.

The anodic methoxylations observed with di- and tri-phenylacetic acids are analogous to the alkoxylation and acetoxylation reactions encountered on electrolysis of *N*-acyl-α-

* Part VI, preceding paper.

amino-acids in alcohols and acetic acid, respectively (Part V). It therefore seemed of interest to extend the present investigation to the use of the latter solvent. Electrolysis of mono- and di-phenylacetic acids in acetic acid solution gave benzyl and diphenylmethyl acetates, the yield of isolated ester being about 40%. By hydrolysing the crude product of the electrolysis of diphenylacetic acid the considerable loss involved in the purification of diphenylmethyl acetate was avoided and diphenylmethanol was obtained in 73% overall yield.

Electrolysis of triphenylacetic acid in acetic acid, and isolation of the product in the usual manner, gave triphenylmethanol directly, and not the acetate, in 50% yield. Most probably triphenylmethyl acetate was formed initially but was hydrolysed during isolation. The extreme ease of hydrolysis of this acetate is well known (Gomberg and Davis, *Ber.*, 1903, **36**, 3926).

To summarise the results described above, phenyl-substitution of acetic acid hinders the normal Kolbe coupling reaction and favours methoxylation and acetoxylation in methanol and acetic acid, respectively. Van der Hoek and Nauta (*loc. cit.*) have suggested that the initial products in the electrolyses of aryl substituted acetic acids are arylmethyl free-radicals which may then react further with the intermediate formation of aryl-substituted methyl peroxides. In our view, however, there is insufficient evidence for the assumption that substituted methyl peroxides are intermediates in the formation of other anodic products.

We do not think the evidence on anodic reactions is as yet sufficiently clear cut to justify any general discussion of mechanism. A good case can, however, be made for the intervention of acetoxyl free-radicals ($CH_3 \cdot CO_2 \cdot$) in the anodic acetoxylations described above. In support of this hypothesis it was found that lead tetra-acetate, which can also furnish acetoxy-radicals (*cf.* Waters, "The Chemistry of Free Radicals," Oxford Univ. Press, 1946), attacks both di- and tri-phenylacetic acid to give, after hydrolysis of the initial products, diphenyl- and triphenyl-methanol respectively in *ca.* 25% overall yields. The anodic reaction can thus be simulated by purely chemical means.

Since toluene and di- and tri-phenylmethane on treatment with lead tetra-acetate in acetic acid give benzyl and diphenyl- and triphenyl-methyl acetates, respectively (Dimroth and Schweizer, *Ber.*, 1923, **56**, 1375), the substitution of these hydrocarbons for the phenylacetic acids in the acetic acid electrolyses has also been examined. In all cases a complex mixture was obtained, possibly owing to occurrence of anodic methylation (*cf.* Fieser, Clapp, and Daubt, *J. Amer. Chem. Soc.*, 1942, **64**, 2002) in addition to acetoxylation. After hydrolysis of the crude products from di- and tri-phenylmethane small amounts of diphenyl- and triphenyl-methanol were isolated. Some alkali-soluble products were also formed on hydrolysis, suggesting that partial acetoxylation of the phenyl groups had occurred during electrolysis. Anodic acetoxylation of an aromatic nucleus, not previously reported, has now been definitely established. We find that when a solution of sodium acetate and naphthalene in acetic acid is electrolysed and the crude product hydrolysed, a 24% yield of α-naphthol is isolated. This recalls the conversion of naphthalene into 1-acetoxynaphthalene in 26% yield on treatment with lead tetra-acetate (*idem, loc. cit.*).

Experimental

In those experiments for which a recovery of starting material is given, allowance for this has been made in calculating the yields of products. In electrolyses in methanol, technical absolute methanol was used as solvent.

Apparatus.—Three cells, "A," "B," and "C," were employed. These consisted of cylindrical glass vessels containing two parallel platinum plates, placed 1—2 mm. apart, as electrodes. In cell "A" the electrodes measured 2·5 × 2·5 cm., in cell "B" 4 × 2·5 cm., and in cell "C" 8 × 5 cm.

Dibenzyl.—(*a*) Phenylacetic acid (13·6 g.) was added to sodium methoxide (from 0·046 g. of sodium) in methanol (30 c.c.), and the solution was electrolysed in cell "A," a current of 0·8 amp. being used, until the electrolyte became slightly alkaline. (During the electrolysis an insoluble material was deposited on the anode and was removed periodically.) The cell contents were neutralised by the addition of acetic acid, and the solvent was then evaporated under reduced pressure. Isolation of the neutral product in the usual way gave dibenzyl (5 g., 55%), b. p.

280—285°, m. p. 51° undepressed on admixture with an authentic specimen, m. p. 51° (Fichter, *Helv. Chim. Acta*, 1939, **22**, 970, gives m. p. 52°).

(*b*) A molten mixture of phenylacetic acid (54·4 g.) and potassium phenylacetate (from 5·44 g. of phenylacetic acid) was electrolysed in cell " B," a current of *ca.* 1 amp. being used, for 12 hours (total amount of electricity passed *ca.* 1 faraday/mole of aryl-acid). This current sufficed to maintain the temperature of the melt at 170—200° without the use of external heating. The cell contents were cooled and extracted with ether. The ethereal solution was washed thoroughly with saturated sodium carbonate solution and dried. On acidification of the alkaline extract, phenylacetic acid (21·0 g.) was recovered. The ethereal solution was evaporated, the residue was hydrolysed, and the product separated into acidic and neutral fractions in the usual way. The acidic fraction gave phenylacetic acid (3·0 g.), m. p. 73° (Found : equiv., 138. Calc. for $C_8H_8O_2$: equiv., 136). Distillation of the neutral fraction gave : (i) Crude benzyl alcohol, b. p. 90—100°/10 mm. The phenylurethane crystallised from light petroleum (b. p. 100—120°) in needles, m. p. 76·5° undepressed on admixture with an authentic specimen, m. p. 76·5°, of the derivative of benzyl alcohol (von Soden and Rojahn, *Ber.*, 1901, **34**, 2809, give m. p. 78°). (ii) Dibenzyl (14 g., 54%), b. p. 100°/0·1 mm., m. p. 51° undepressed on admixture with an authentic specimen.

Methyl Triphenylmethyl Ether.—Triphenylacetic acid (8·64 g.) was added to sodium methoxide (from 46 mg. of sodium) in methanol (300 c.c.), and the solution was electrolysed in cell " B," a current of 1·5 amp. being used, until alkaline. The solvent was evaporated under reduced pressure, the residue was dissolved in ether, and the solution was washed with N-sodium hydroxide solution, dried, and evaporated. Crystallisation of the residue from methanol gave methyl triphenylmethyl ether (5·0 g.) as plates, m. p. 82·5° undepressed on admixture with an authentic specimen (Friedel and Crafts, *Ann. Chim.*, 1884, **1**, 503, give m. p. 82°).

Benzyl Acetate.—A solution of phenylacetic acid (20·0 g.) and sodium acetate (8·2 g.) in glacial acetic acid (180 g.) was electrolysed in cell " B " for 19·5 hours, a current of 2 amp. being used (electricity passed *ca.* 10 faradays/mole of aryl acid). The solvent was evaporated under reduced pressure, the residue was dissolved in ether, and the ethereal solution was washed with saturated sodium carbonate solution and dried. On acidification of the alkaline extract, phenylacetic acid (8·6 g.) was recovered. The ethereal solution was evaporated and the residue distilled giving benzyl acetate (5·3 g.), b. p. 130—135°/64 mm., n_D^{21} 1·4975 (Found : sap. equiv., 152. Calc. for $C_9H_{10}O_2$: sap. equiv., 150). Hydrolysis of the ester (2·0 g.) gave benzyl alcohol (1·0 g.), n_D^{21} 1·5386 (Brühl, *Annalen*, 1888, **200**, 190, gives n_D^{20} 1·5396). The phenylurethane, prepared in 80% yield, had m. p. 76·5° undepressed on admixture with an authentic specimen.

Diphenylmethyl Acetate and Diphenylmethanol.—(*a*) A solution of diphenylacetic acid (10·6 g.) and anhydrous sodium acetate (4·1 g.) in glacial acetic (60 g.) was electrolysed in cell " B " for 3·5 hours a current of 2 amp. being used (electricity passed *ca.* 5 faradays/mole of aryl acid). Evaporation of the solvent and isolation of the neutral product gave diphenylmethyl acetate, which crystallised from light petroleum (b. p. 40—60°) at −30° in prisms (4·2 g.), m. p. 40° (Found : sap. equiv., 227. Calc. for $C_{15}H_{14}O_2$: sap. equiv., 226) (Bodroux, *Bull. Soc. chim.*, 1899, **21**, 290, gives m. p. 40°). Hydrolysis of the acetate (3·0 g.) gave diphenylmethanol which crystallised from light petroleum (b. p. 40—60°) in needles (2·6 g.), m. p. 67° undepressed on admixture with an authentic specimen (Linnemann, *Annalen*, 1865, **133**, 9, gives m. p. 68°).

(*b*) A solution of diphenylacetic acid (53·0 g.) and anhydrous sodium acetate (20·5 g.) in glacial acetic acid (300 g.) was electrolysed in cell " C " for 4 hours, a current of 8·0 amp. being used (electricity passed *ca.* 5 faradays/mole of aryl acid). Isolation of the product in the usual manner gave (i) recovered diphenylacetic acid (16·0 g.) and (ii) crude diphenylmethyl acetate, which was heated under reflux for 1 hour with excess of aqueous-alcoholic potassium hydroxide solution (10% w/v). Isolation of the neutral product and crystallisation from light petroleum (b. p. 40—60°) gave diphenylmethanol (25 g.) as needles, m. p. and mixed m. p. 67°.

(*c*) A solution of diphenylacetic acid (2·12 g.) and lead tetra-acetate (11·1 g.) in glacial acetic acid (25 c.c.) was heated on a steam-bath for 3 hours. The mixture was then cooled and diluted with ether. The ethereal layer was washed successively with water, 2N-nitric acid, and saturated sodium carbonate solution, dried, and evaporated. The residue was hydrolysed. Isolation of the crude product (1·0 g.) with ether and crystallisation from light petroleum (b. p. 60—80°)–carbon tetrachloride gave diphenylmethanol (0·5 g., 27%) as needles, m. p. 67° undepressed on admixture with an authentic specimen.

Triphenylmethanol.—(*a*) A solution of triphenylacetic acid (14·4 g.) and anhydrous sodium acetate (24·6 g.) in glacial acetic acid (360 g.) was electrolysed in cell " C " for 1·5 hours with a current of 7·0 amp. (*ca.* 8 faradays/mole of aryl acid). The solution was evaporated under

reduced pressure, the residue was extracted with ether, and the extract was washed with aqueous sodium hydroxide solution (10% w/v). On acidification of the alkaline washing triphenylacetic acid (3·7 g.) was recovered. The ethereal solution was dried and evaporated, and the residue was crystallised from carbon tetrachloride, giving triphenylmethanol (4·8 g.), m. p. 161° undepressed on admixture with an authentic specimen, m. p. 161°. The carbon tetrachloride mother-liquors were evaporated and the residue was hydrolysed. Separation of the neutral fraction and crystallisation from carbon tetrachloride gave a further small quantity (1·0 g.) of triphenylmethanol. Evaporation of the mother-liquors gave an oil which with Brady's reagent yielded benzophenone 2 : 4-dinitrophenylhydrazone (0·8 g.), m. p. 238° undepressed on admixture with an authentic specimen.

An authentic specimen of triphenylmethyl acetate on treatment with water and with alcohol gave triphenylmethanol and ethyl triphenylmethyl ether, respectively, in almost quantitative yields (*cf.* Gomberg and Davis, *Ber.*, 1903, **36**, 3926).

(*b*) A solution of triphenylacetic acid (1·44 g.) and lead tetra-acetate (10 g.) in acetic acid (20 c.c.) was heated on a steam-bath for 4 hours. 2N-Nitric acid was added and the mixture was extracted with ether. The extract was washed successively with 2N-nitric acid, 2N-sodium hydroxide, and water, dried, and evaporated. Crystallisation of the residue from alcohol and then from carbon tetrachloride gave triphenylmethanol (0·3 g., 23%), m. p. 159—160° undepressed on admixture with an authentic specimen.

Electrolyses of Acetic Acid in the Presence of Toluene and Di- and Tri-phenylmethane.—Solutions of anhydrous sodium acetate (0·05M) in glacial acetic acid were electrolysed in cell " C " in the presence of toluene (0·05M), diphenylmethane (0·05M), and triphenylmethane (0·02M) severally. The electrolyses were continued until *ca.* 15 faradays/mole of hydrocarbon had been passed. Isolation and hydrolysis of the products in the usual way (sap. equiv., 170, 220—250, and 358, respectively) and separation of the neutral fractions (*ca.* 16, 55, and 40% yields, respectively, based on hydrocarbon) gave complex intractable mixtures from which, in the experiments with di- and tri-phenylmethane, small amounts of diphenyl- and triphenyl-methanol, respectively, were isolated. Hydrolysis of the crude products from these two hydrocarbons also gave small amounts (*ca.* 5 and 20%, respectively, based on hydrocarbon) of dark brown alkali-soluble materials.

α-*Naphthol.*—A solution of naphthalene (6·4 g.) and anhydrous sodium acetate (0·9 g.) in glacial acetic acid (30 g.) was electrolysed in cell " A " for 8·0 hours, a current of 0·5 amp. being used (3 faradays/mole of naphthalene). The dark brown contents of the cell were extracted with ether, and the extract was washed with sodium carbonate solution, dried, and evaporated. The residue was hydrolysed with aqueous alcoholic alkali. From the non-hydrolysable fraction naphthalene (0·5 g.), m. p. and mixed m. p. 80°, was recovered by chromatographic adsorption on alumina from benzene solution. The alkali-soluble product (4·7 g.) was distilled, giving crude α-naphthol (1·6 g., 24%), m. p. 80—85°. Sublimation under reduced pressure, followed by two crystallisations from light petroleum (b. p. 40—60°), containing a trace of ether, gave α-naphthol as needles, m. p. 95·5° undepressed on admixture with an authentic specimen.

Chromatographic purification of a small portion of the crude α-naphthol, m. p. 80—85°, on alumina from benzene solution, followed by treatment of the chromatogram with diazotised sulphanilic acid (*cf.* Zechmeister and Cholnoky, " The Principles and Practice of Chromatography," London, 1941, p. 87), indicated the presence of some β-naphthol in addition to the α-isomer.

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694. *The Kinetics and Mechanisms of Nucleophilic Displacements in Allylic Systems. Part III.* The Reactions of* 3 : 3 : 3-*Trichloro-2-methylprop-1-ene with Nucleophilic Reagents.*

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The compound $CCl_3 \cdot CMe{:}CH_2$ reacts with sodium thiophenoxide in ethyl alcohol to form the product of substitution with rearrangement, $CCl_2{:}CMe \cdot CH_2 \cdot SPh$. This process, being kinetically of the second order, is a further example of the S_N2' mechanism, and the rate is somewhat faster than that of the corresponding reaction of 3 : 3-dichloroprop-1-ene.

1-METHYLALLYL CHLORIDE reacts bimolecularly with alcoholic sodium ethoxide to give the product of normal (S_N2) substitution (cf. Catchpole, Hughes, and Ingold, *J.*, 1948, 11). In Parts I and II (*locc. cit.*), however, it has been shown that the presence of an α-chloro-substituent, as in 3 : 3-dichloroprop-1-ene (*i.e.*, 1-chloroallyl chloride) is unfavourable to the S_N2 mechanism, and promotes bimolecular substitution with anionotropic rearrangement (S_N2'). As a result, therefore, the S_N2 and S_N2' mechanisms of substitution contribute nearly equally to the reactions of this compound with ethoxide, phenoxide, and thiophenoxide ions. It was suggested (cf. Hughes and Ingold, *J. Chim. phys.*, 1948, **45**, 241) that the S_N2' reaction is favoured, in such an example, by the inductive influence of the $CHCl_2$ group, which displaces the screen of unsaturation electrons in such a way as to make less difficult the attack of a nucleophilic reagent on the unsaturated carbon atom, as may be represented thus : $EtO^- \curvearrowright CH_2{:}CH \cdot CHCl_2 \curvearrowright \longrightarrow$.

It would be a consequence of this interpretation that the CCl_3 group should be still more effective in promoting reaction by this mechanism, the more so since S_N2 attack on this group is still more difficult. Kirrmann and Jacob (*Bull. Soc. chim.*, 1940, **7**, 586) have indeed recorded that the compounds $CCl_3 \cdot CMe{:}CH_2$ and $CCl_2{:}CMe \cdot CH_2Cl$ react, the former much less readily than the latter, with water, sodium acetate, potassium *p*-nitrobenzoate, and sodium ethoxide, to give, in each case in good yield, the product expected from the second isomer (*e.g.*, $CCl_2{:}CMe \cdot CH_2 \cdot OEt$ in the reaction of either isomer with sodium ethoxide). Since these authors made no kinetic measurements, they were unable to discuss adequately the mechanism involved in the anionotropic rearrangements which they were observing in the reactions of $CCl_3 \cdot CMe{:}CH_2$. For this reason, we have examined the kinetics and products of the reaction of this compound with sodium thiophenoxide in ethyl alcohol. The reaction is kinetically of the second order, and the first equivalent of chloride is released from the compound considerably more rapidly than the second and third. The velocity constant at 24·7° was found to have the value $k_2 = 6{\cdot}2 \times 10^{-3}$ l. mole^{-1} min.$^{-1}$,† and the energy of activation in the range 24·7—64·9° was 20·3 kcal. These values indicate that the reaction occurs more readily than that of the S_N2' component of the similar reaction of 3 : 3-dichloroprop-1-ene (k_2 at 24·7°, $2{\cdot}5 \times 10^{-3}$; $E = 21{\cdot}2$ kcal.). From 8 g. of trichloride, with the equivalent quantity of sodium thiophenoxide, there was obtained in 64% yield the compound $CCl_2{:}CMe \cdot CH_2 \cdot SPh$, identical in properties with a sample obtained similarly from $CCl_2{:}CMe \cdot CH_2Cl$. It is concluded, therefore, that $CCl_3 \cdot CMe{:}CH_2$ reacts with thiophenoxide ion almost exclusively by S_N2' displacement of chloride.

3 : 3-Dichloroprop-1-ene thus reacts with thiophenoxide ion to give the product of anionotropic rearrangement, at about half the rate found for $CCl_3 \cdot CMe{:}CH_2$; the activation energy for the reaction of the former compound is correspondingly slightly higher. A similar difference in reactivity by this mechanism is found for the reaction with sodium ethoxide. The CCl_3 group, as compared with the $CHCl_2$ group, would be expected to favour the S_N2' reaction by an even greater factor; but in the present example, the additional 2-methyl substituent has an opposing effect, which, as might be expected, partly cancels the influence of the third chlorine substituent.

* Parts I and II, *J.*, 1952, 3325, 3331.

† All velocity coefficients given in this paper are in these units.

We hope in due course to study the similar reactions of 3 : 3 : 3-trichloroprop-1-ene. The compound which has customarily been assigned this structure (Victoria, *Rec. Trav. chim.*, 1905, **24**, 280; Kharasch, Rossin, and Fields, *J. Amer. Chem. Soc.*, 1941, **63**, 2558), although moderately reactive with sodium ethoxide at 65°, hardly reacts with sodium thiophenoxide under the same conditions. Substitution reactions in such circumstances are usually some 10^2—10^3 more rapid with sodium thiophenoxide than with sodium ethoxide, as, for example, we have shown herein for $CCl_3 \cdot CMe{:}CH_2$. We therefore concluded that the compound usually described as 3 : 3 : 3-trichloroprop-1-ene is probably 1 : 1 : 2-trichloroprop-1-ene, as seemed not unlikely, since this compound might be formed from the addition of hydrogen chloride to 1 : 1-dichloroallene, and both of these substances are reported (Kharasch, Rossin, and Fields, *loc. cit.*) as by-products in the usual preparation of this trichloropropene. During the course of the experiments described herein, our attention was called to an abstract (*Chem. Abstr.*, 1952, **46**, 1957) of a paper by Nesmayanov, Freidlina, and Firstov (*Doklady Akad. Nauk. S.S.S.R.*, 1951, **78**, 717), in which chemical evidence is given of the correctness of this view (cf. also Ladd and Shinkle, U.S.P. 2,561,516).

Experimental

(a) *Preparation of Trichlorobutenes.*—Jacob (*Bull. Soc. chim.*, 1940, **7**, 584) described the synthesis, as well as the proofs of structure, of $CCl_3 \cdot CMe{:}CH_2$ and $CCl_2{:}CMe \cdot CH_2Cl$. Although poor yields of pure product were obtained by this method, it proved in our hands more satisfactory than that of Price and Marshall (*J. Org. Chem.*, 1943, **8**, 532). Anhydrous chlorobutol was dehydrated in small batches by phosphoric oxide in the presence of dimethylaniline, and the combined product was dissolved in ether, washed with sodium carbonate and then with water, dried ($CaCl_2$), and fractionated in a helix-packed column, giving 3 : 3 : 3-trichloro*iso*butene (13 g. from 400 g. of chlorobutol), n_D^{25} 1·4760, b. p. 52—53°/45 mm., which appeared to be kinetically pure. Its isomer, 1 : 1 : 3-trichloro*iso*butene, was obtained in good yield as a subsequent fraction, b. p. 75°/45 mm., n_D^{25} 1·4961.

(b) *Products.*—1 : 1 : 3-trichloro*iso*butene (22 g.) was gradually added to 200 ml. of 0·6N-sodium thiophenoxide in alcohol. After the reaction mixture had been kept overnight, the product was extracted with pentane, and the extract was washed with water, dried, and fractionated, giving 13 g. of 1 : 1-*dichloro*-2-*methyl*-3-*thiophenoxyprop*-1-*ene*, b. p. 112—114°/*ca.* 0·7 mm., n_D^{25} 1·5853 [Found: C, 51·1; H, 4·5; S, 14·1; Cl (determined by reaction with sodium in ethylene glycol at 200°), 31·0. $C_{10}H_{10}SCl_2$ requires C, 51·5; H, 4·3; S, 13·7; Cl, 30·5%].

By a similar method, there were obtained, from 3 : 3 : 3-trichloro*iso*butene (8 g.) and an equivalent quantity of sodium thiophenoxide, 7·5 g. of 1 : 1-dichloro-3-phenylthio*iso*butene, b. p. 107—113°/*ca.* 0·5 mm., n_D^{25} 1·5863, of which a middle fraction (4·5 g.) had b. p. 111—112°/*ca.* 0·5 mm., n_D^{25} 1·5857 (Found: C, 52·1; H, 4·3; S, 13·3; Cl, 29·9%). Both these compounds reacted slowly at the same rate with sodium thiophenoxide; the kinetics of this reaction are outlined later, but the products have not been further investigated.

(c) *Kinetics.*—Reagents and methods were as described in Parts I and II (*locc. cit.*). Herewith are the results of a typical kinetic run. 3 : 3 : 3-Trichloro*iso*butene (0·1150M) was made up in 0·319N-sodium thiophenoxide. Samples (5 ml.) were removed from the thermostat (24·7°) at appropriate intervals, added to 20 ml. of ice-cold 0·1153N-hydrochloric acid, and rapidly back-titrated with 0·02716N-sodium hydroxide (bromophenol-blue). The initial sample was allowed 50 minutes to warm to thermostat temperature.

Time (min.)	0	70	166·5	250	338	368	402	442	∞
RCl_3 destroyed (ml. of 0·02716N-NaOH)	0·00	1·95	4·35	6·10	7·70	8·50	8·60	9·50	19·20
10^3k_2	—	5·1	5·2	5·3	5·3	5·6	5·2	5·5	—

The mean velocity coefficient, $k_2 = 5{\cdot}3 \times 10^{-3}$ for [NaSPh] = 0·319, is only slightly raised, owing apparently to the usual small negative salt effect, by changing the concentration of thiophenoxide to 0·164 ($k_2 = 6{\cdot}2 \times 10^{-3}$). Solvolysis is negligibly slow. Hence the reaction is of the second order ($d[Cl^-]/dt = k[RCl_3][SPh^-]$).

At 64·9°, the corresponding second-order rate-coefficient ([NaSPh] = 0·326) was 0·314. It was necessary to show that the stage of the reaction under kinetic observation resulted in the release of only one equivalent of chlorine; for this would be the result of an S_N2' reaction, whereas normal S_N2 substitution would be expected to lead to the liberation of all the chlorine in the molecule, as in the reactions of chloroform with nucleophilic reagents (Huntress, " Organic

Chlorine Compounds," Wiley and Sons, New York, 1948, p. 552). The above second-order velocity coefficients have been calculated by using the usual formula

$$k_2 = 2{\cdot}303\,\{\log_{10} b(a - x)/a(b - x)\}/t(a - b)$$

where a is the measured initial concentration of sodium thiophenoxide, and b is the molar concentration of trichlorobutene. The constancy of these values indicates that only 1 equiv. of chlorine is released in the rate-determining process, but attempts to measure an experimental value for the release of chlorine at complete reaction indicated a slow further release of chlorine, as shown in the following results, for $CCl_2{\cdot}CMe{:}CH_2$ = 0·101M and NaSPh = 0·326N :

Time (min.)	0	5·0	11·0	24·5	33·5	41·4	137	214	410	4330
Release of chloride equiv. per mol. of $CCl_2{\cdot}CMe{:}CH_2$	0·348 *	0·582	0·747	0·912	0·968	1·015	1·166	1·280	1·431	1·903

* This represents reaction occurring in the time (5 mins.) required for warming to the temperature (64·9°) of the thermostat.

This further release of chloride was not the result of a part of the initial process proceeding by the S_N2 mechanism, but of the subsequent reaction of the product, $CCl_2{:}CMe{\cdot}CH_2{\cdot}SPh$, formed by the initially rapid substitution. The following experiment shows the rate of reaction of $CCl_2{:}CMe{\cdot}CH_2{\cdot}SPh$ (0·0450M) with sodium thiophenoxide (0·1491N) at 64·9°.

Time (min.)	109	196	292	1223	1700	2800
Release of chloride, equiv. per mol. of $CCl_2{:}CMe{\cdot}CH_2{\cdot}SPh$	0·170	0·272	0·374	0·942	1·094	1·284

The initial second-order rate-coefficient for the release of the first equiv. of chloride from this compound ($k_2 = 6{\cdot}0 \times 10^{-3}$, based on the release of 2 equiv. of chloride at completion of reaction), corresponds well with the value ($k_2 = 5{\cdot}2 \times 10^{-3}$) obtained from the above data for $CCl_2{\cdot}CMe{:}CH_2$, considering the rate of release of the *second* equivalent of chloride, as a proportion of the release of the last 2 equiv. of chloride. The initial S_N2' reaction of $CCl_2{\cdot}CMe{:}CH_2$ is, however, some 50 times faster than the subsequent decomposition of the product, which does not, therefore, interfere with the determination of the velocity of the former reaction. It is concluded that the second-order reaction, which results in the liberation of the first equivalent of chloride from $CCl_2{\cdot}CMe{:}CH_2$, leads to formation of $CCl_2{:}CMe{\cdot}CH_2{\cdot}SPh$, and is therefore an example of the S_N2' mechanism.

The following shows the rate of development of chloride from $CCl_2{\cdot}CMe{:}CH_2$ (0·0305M) with sodium ethoxide (0·514N) in ethyl alcohol at 64·9°. Samples (5·03 ml.) were titrated with 0·0100N-silver nitrate.

Time (min.)	0	965	1225	2340	2720	4220	∞
Titre (ml.)	0·00	5·32	6·30	9·44	10·44	12·14	15·24
10^4k_2	—	8·3	8·2	8·0	8·1	7·2	—

Solvolysis of the compound was found to be considerably slower at this temperature, as shown by the rate of development of acid from 5·0-ml. samples of $CCl_2{\cdot}CMe{:}CH_2$ (0·0250M) in ethyl alcohol at 64·9°, titrated in alcohol with sodium hydroxide, lacmoid being used as indicator :

Time (min.)	0	200	315	2780	4545	∞
Titre (ml. of 0·02716N-NaOH)	0·11	0·20	0·27	0·80	1·18	4·60

Hence the reaction with sodium ethoxide is bimolecular, and, since Kirrmann and Jacob (*loc. cit.*) showed that the product involved rearrangement, this reaction also is to be classified as S_N2'. Its rate, as for the reaction with thiophenoxide, is faster than that recorded in Part I (*loc. cit.*) for the S_N2' component of the reaction of $CHCl_2{\cdot}CH{:}CH_2$ with sodium ethoxide ($k_2 = 3{\cdot}6 \times 10^{-4}$).

(d) "*Trichloropropene.*"—The product of dehydration of 1 : 1 : 1-trichloropropan-2-ol with phosphoric oxide gave a product, b. p. 116—118°/762 mm., n_D^{25} 1·4790 (Kharasch, Rossin, and Fields, *loc. cit.*, record, for a product prepared similarly, n_D^{20} 1·4827). This material (0·0279M) reacted at 64·9° with sodium ethoxide (0·471N) to release 1 equiv. of chloride in 500 min., 2 equiv. in 1600 min., and 2·7 equiv. at completion of reaction (1 week at 75°). With sodium thiophenoxide (0·155N) at 64·9°, less than 0·1 equiv. of chloride was released in 500 minutes, and hence the rate of reaction of this material with thiophenoxide is slower than that with ethoxide. The latter reaction, therefore, is most probably not a substitution, but an elimination, and the compound is probably $CCl_2{:}CCl{\cdot}CH_3$ (cf. Nesmayanov, Freidlina, and Firstov, *loc. cit.*). Attempted dehydration of trichloropropan-2-ol by phosphoric oxide in the presence of

quinoline gave only material of b. p. 106°, n_D^{25} 1·4548. This may be the substance described by Kharasch *et al.* (*loc. cit.*) as dichloroallene, b. p. 52—55°/103 mm., n_D^{25} 1·4650; on treatment with sodium ethoxide in ethyl alcohol, the solution immediately darkened, and sodium chloride was precipitated, but only a quarter of the amount of chlorine expected for the above compound was detected, either immediately or after 4 days at room temperature.

We are indebted to Professors E. D. Hughes, D.Sc., F.R.S., and C. K. Ingold, D.Sc., F.R.S., for continued encouragement. We thank Mr. E. Grayson for technical assistance. Analyses are due to Drs. Weiler and Strauss, of Oxford, and Mr. E. Winter of this Department.

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695. *The Detection of Deoxy-sugars, Glycals, and Methyl Pentoses in Paper Partition Chromatography.*

By J. T. Edward and Deirdre M. Waldron.

Colour tests have been found by which deoxy-sugars, glycals, and methyl pentoses may be distinguished from other sugars or sugar derivatives on paper chromatograms. By application of these tests the presence of fucose in serum and urinary mucoprotein has been demonstrated (Waldron, *Nature*, in the press). Some limitations and advantages in conducting spot tests on paper are discussed.

Methyl pentoses and deoxy-sugars may be located on paper chromatograms by spraying them with various reagents (Partridge, *Biochem. J.*, 1948, **42**, 238; *Biochem. Soc. Symposia*, 1950, No. 3, p. 52; Forsyth, *Nature*, 1948, **161**, 239; Hough, Jones, and Wadman, *J.*, 1950, 1702) but researches in progress in our laboratories indicated the need for more specific reagents for distinguishing them from the other reducing sugars. Buchanan, Dekker, and Long (*J.*, 1950, 3162) applied the Feulgen and the Dische reaction to the detection of deoxyribonucleosides, but the methods were inconvenient and relatively insensitive. More recently Buchanan (*Nature*, 1951, **168**, 1091) has employed a spray of cysteine in 3N-sulphuric acid to reveal the presence of deoxy-sugars and deoxyglycosides.

Although the usual aldoses and ketoses are oxidised by periodate to the one-carbon fragments formaldehyde and formic acid (Jackson, "Organic Reactions," 1944, vol. II, p. 345), compounds having a carbon chain lacking some vicinal hydroxyl groups will also yield larger fragments possessing active methyl or methylenic groups. Thus, methyl pentoses give acetaldehyde (Nicolet and Shinn, *J. Amer. Chem. Soc.*, 1941, **63**, 1456), deoxy-sugars malondialdehyde (cf. Manson and Lampen, *J. Biol. Chem.*, 1951, **191**, 95), and deoxypyranosides and deoxy-alcohols such as 2-deoxy-D-dulcitol or 1 : 2-dideoxy-galactose should also yield products with the $\cdot CH_2 \cdot CHO$ grouping. This grouping gives a blue colour with nitroprusside in the presence of secondary amines (Rimini, *Chem. Zentr.*, 1898, II, 277; Lewin, *Ber.*, 1899, **32**, 3308; Neuberg, *Biochem. Z.*, 1915, **71**, 150; Neuberg and Kerb, *ibid.*, 1918, **92**, 96; Fearon and Boggust, *Analyst*, 1951, **76**, 667), and we have found that the compounds mentioned above may be revealed as blue zones when chromatograms are sprayed with aqueous periodate (cf. Buchanan, Dekker, and Long, *loc. cit.*) followed by a solution of sodium nitroprusside and piperazine in aqueous alcohol. Threonine, which is oxidised by periodate to acetaldehyde (Martin and Synge, *Biochem J.*, 1941, **35**, 94), can be distinguished by this test from the other amino-acids. Glycals also react; they are probably oxidised to dialdehydes having the $\cdot O \cdot CH{=}CH \cdot CHO$ grouping; and it is likely that the positive reaction, like those of acraldehyde and cinnamaldehyde (Lewin, *loc. cit.*), depend on the initial addition of the secondary amine to the double bond so that the $\cdot CH_2 \cdot CHO$ grouping is formed.

Unoxidised 2-deoxy-sugars react feebly with nitroprusside–piperazine, presumably because of the small proportion present in the straight-chain form.

Deoxy-sugars and glycals can be distinguished from methyl pentoses by the deep yellow zones which they give when the chromatogram is sprayed with an acidic solution of *p*-nitroaniline after periodate oxidation. This colour is believed to be due to a condensation of malondialdehyde (which can be furnished by hydrolysis of the ·O·CH=CH·CHO grouping of the oxidised glycal) with the aromatic amine, analogous to the condensations of glutacondialdehyde [Maier-Bode and Altpeter, "Das Pyridin und seine Derivate," W. Knapp, Halle (Saale), 1934, p. 18], which is a vinylogue of malondialdehyde. This test is positive also for deoxyglycosides, including guanine deoxyribofuranoside, which though not initially oxidised by periodate (Brown and Lythgoe, *J.*, 1950, 1990) probably first undergoes hydrolysis to deoxyribose on the paper.

A second test by which glycals and deoxy-sugars can be distinguished from methyl pentoses consists in spraying the chromatogram with an acid solution of *p*-dimethylaminobenzaldehyde or ninhydrin. On gentle heating, the former compounds give rise to blue or grey zones, the glycals showing an initial pink colour. On more prolonged heating pentoses and ketoses form coloured zones, but aldohexoses and methyl pentoses do not (cf. Partridge, *loc. cit.*). It is probable that the condensation of the *p*-dimethylaminobenzaldehyde takes place with products resulting from the acid-catalysed rearrangement of the deoxy-sugars or glycals (cf. Deriaz, Stacey, Teece, and Wiggins, *J.*, 1949, 1222; Allerton, Overend, and Stacey, *J.*, 1952, 255; Newth, *Adv. Carbohydrate Chem.*, 1952, **2**, 85), since these products (kindly furnished by Professor Stacey and Dr. Shafizadeh) react as do the sugars, whereas aldol and other compounds containing the ·CH_2·CHO group fail to give a perceptible colour.

Buchanan's cysteine–sulphuric acid reaction (*loc. cit.*) probably involves a preliminary rearrangement of the deoxy-sugars and is positive also for glycals.

Specific tests for glycals are furnished by spraying chromatograms with ethanolic hydrochloric acid which on gentle warming gives zones initially pink but changing to brown; or with alcoholic ferric chloride which gives brown zones changing to black. Since the glycals are easily separable from their corresponding deoxy-sugars by paper chromatography, these tests may prove useful in following their reactions.

The tests described above are all much more sensitive when carried out on filter paper rather than in solution (cf. Feigl, "Specific and Special Reactions for Use in Qualitative Analysis," Nordemaa, New York, 1940, p. 162), except in the case of some very volatile compounds. Thus nitromethane reacts like acetaldehyde with nitroprusside–piperazine in solution but unlike acetaldehyde cannot be tested on paper, because it evaporates before the slow reaction takes place. The retention of the more volatile acetaldehye on paper, which recalls the difficulty frequently encountered in removing from paper chromatograms the last traces of polar developing solvents, is probably due to solution in the adsorbed water, or to direct hydrogen bonding to cellulose.

A second advantage in conducting spot tests on paper lies in the generally increased rate of reactions. Thus 2-deoxy-D-glucose, because of the *trans*-α-glycol system of its pyranose ring, is oxidised more slowly than 2-deoxy-D-galactose in dilute solution (cf. Jackson, *loc. cit.*), and requires about two hours before the maximum colour is attained after addition of the nitroprusside–piperazine solution. However, on paper maximum colour is obtained after 10—15 minutes' oxidation. It seems likely that after the periodate solution has been sprayed on the chromatogram, evaporation of the solvent results in an extremely concentrated solution, in which oxidation takes place more rapidly. Such an effect would perhaps explain the observation of Hough (*Nature*, 1950, **165**, 400) that on paper even polyhydric alcohols react with ammoniacal silver nitrate.

Experimental

Unless otherwise stated, the paper chromatograms were developed by the ascending technique, with pyridine–amyl alcohol–water as solvent (Werner and Odin, *Uppsala Läk. Forsch.*, 1949, **1/2**, 69) and Whatman No. 1 filter paper.

Test A. Periodate Oxidation, followed by Treatment with Nitroprusside–Piperazine.—The dried paper chromatograms were sprayed lightly with saturated aqueous sodium metaperiodate (1 vol.) diluted with water (2 vols.). After 10 minutes at room temperature, a solution of

saturated aqueous sodium nitroprusside (1 vol.), water (3 vols.), and ethanol saturated with piperazine (20 vols.), was sprayed on the paper. Methyl pentoses, deoxy-sugars, and glycals gave rise to blue zones in 5—10 minutes, and thereafter slowly faded. The sensitivity to deoxy-sugars was slightly improved by adding to the second spray an equal volume of 1% ethylene glycol in methanol, in order to destroy excess of periodate. The minimum quantity detectable in spot tests is shown in the Table. On chromatograms, because of diffusion of the zones, sensitivity was diminished five- to ten-fold.

Secondary bases such as piperidine and diethylamine (cf. Rimini, *loc. cit.*; Lewin, *loc. cit.*) could be substituted for piperazine if this test was carried out in solution. However, they were unsatisfactory for tests on paper because of their volatility. Samples of diethylamine frequently gave rise to a blue colour with nitroprusside alone, presumably because they had undergone some oxidation to acetaldehyde; this compound was detected also in old specimens of triethylamine and diethylaminoethanol.

Test B. Periodate Oxidation, followed by Condensation with p-*Nitroaniline.*—After periodate oxidation the chromatograms were sprayed with a solution made up of 1% *p*-nitroaniline in ethanol (4 vols.) and concentrated hydrochloric acid (1 vol.). Deep yellow spots rapidly appearing against the pale yellow background indicated deoxy-sugars and glycals; these could be more easily detected in ultra-violet light as yellow fluorescent zones against a brown background. When the chromatograms were sprayed with 5% methanolic sodium hydroxide, the zone became green; the sensitivity in spot tests is shown in the Table.

Sensitivity (in μg.) of colour reactions for methyl pentoses, deoxy-sugars, and glycals.

Sugar	Test A	Test B	Test C	Test D
Fucose	4	—	—	—
Rhamnose	1	—	—	—
2-Deoxy-D-ribose	2	0·1	0·1	—
2-Deoxy-D-glucose	2	0·1	0·2	—
2-Deoxy-D-galactose	1	0·1	0·2	—
3-Deoxy-L-xylose	1	0·1	7	—
α-Methyl-2-deoxy-D-ribopyranoside	10	0·1	0·1	—
α-Methyl-2-deoxy-D-galactopyranoside	50	0·1	0·1	—
β-Methyl-3-deoxy-L-xyloside	—	3	7	—
β-Guanine-2-deoxy-D-ribofuranoside	—	1	0·5	—
2-Deoxy-D-dulcitol	1	—	—	—
1 : 2-Dideoxy-D-galactose	5	—	—	—
D-Ribal	0·2	0·1	0·7	0·1
D-Glucal	1	0·2	0·2	0·1
D-Galactal	1	0·1	0·1	0·1
3 : 4 : 6-Triacetyl D-glucal	—	—	—	—

Other methods which were employed to reveal the malondialdehyde resulting from the oxidation of deoxy-sugars were: spraying with alcoholic ferric chloride (cf. Claisen, *Ber*, 1903, **36**, 3664); spraying with diazotised *p*-anisidine (Sanger and Tuppy, *Biochem. J.*, 1951, **49**, 463) and making alkaline with ammonia fumes (cf. Claisen, *loc. cit.*); and exposure to sulphur dioxide followed by a spray of Schiff's reagent (cf. Buchanan, Dekker, and Long, *loc. cit.*). However, none of these methods was as sensitive as the one above.

Test C. Treatment with p-*Dimethylaminobenzaldehyde in Acid.*—Chromatograms were sprayed with a mixture of 1% *p*-dimethylaminobenzaldehyde in ethanol (4 vols.) and concentrated hydrochloric acid (1 vol.) and heated in an oven at 90°. In 30 seconds deoxypentoses, deoxypentosides, and D-ribal had given rise to bluish- or purplish-grey spots; deoxyhexoses, deoxyhexosides, glucal, and galactal had given pinkish-grey spots. 3-Deoxy-L-xylose and β-methyl-3-deoxy-L-xyloside responded slightly more slowly (cf. Allerton, Overend, and Stacey, *loc. cit.*), to give grey colours. When heating was prolonged for 2 minutes, xylose and arabinose (1—2 μg.) gave grey zones. The sensitivity of the test for materials spotted on paper is shown in the Table. Substitution of ninhydrin for *p*-dimethylaminobenzaldehyde resulted in a test of the same sensitivity, but with more bluish colours.

Test D. Treatment with Alcoholic Hydrochloric Acid.—Chromatograms were sprayed with concentrated hydrochloric acid (1 vol.) diluted with ethanol (4 vols.). On heating in an oven at 90°, pink zones changing rapidly to brown indicated the presence of glycals. The spray of alcoholic ferric chloride was slightly less sensitive.

Chromatography of Glycals and Deoxy-sugars.—Glycals and deoxy-sugars were submitted to ascending chromatography at 20° with Partridge's solvent system butanol–acetic acid–water (*loc. cit.*), and located with *p*-dimethylaminobenzaldehyde spray. The R_F values were: D-

galactal, 0·54; D-glucal, 0·61; D-ribal, 0·77; 2-deoxy-D-galactose, 0·32; 2-deoxy-D-glucose, 0·35; 2-deoxy-D-ribose, 0·45.

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696. *The Hydroxynaphthoate Series. Part I. A Synthesis of 4-Hydroxynaphthoic Acid and its Simple Esters.*

By G. W. K. CAVILL and J. R. TETAZ.

The synthesis of some potentially fungistatic 4-hydroxynaphthoates is described. The parent acid is obtained by direct oxidation of the aldehyde with alkaline silver oxide, and the *n*-alkyl esters are synthesised by an indirect route *via* 4-benzyloxynaphthaldehyde and the corresponding acid.

THE inhibitory action of the esters of 4-hydroxybenzoic acid against micro-organisms including bacteria, moulds, and yeasts is well known; more recently these compounds have found considerable use as preservatives, and further systematic investigations on the fungistatic activity of the simple and substituted *p*-hydroxybenzoates have been undertaken (Cavill and Vincent, *J. Soc. Chem. Ind.*, 1947, **66**, 175; Cavill, Phillips, and Vincent, *ibid.*, 1949, **68**, 12). Likewise the fungistatic activity of the *p*-aminobenzoates has been demonstrated (Cavill and Vincent, *ibid.*, p. 189) and similarly it is intended to investigate the 4-hydroxynaphthoates.

The present communication reports a new synthesis of 4-hydroxynaphthoic acid and its simple esters.

4-Hydroxynaphthoic acid was first obtained by Heller (*Ber.*, 1912, **45**, 675) by fusion of 4-hydroxynaphthaldehyde with potassium hydroxide. The naphthoic acid was readily decarboxylated; even heating it in aqueous solution for a short time caused evolution of carbon dioxide. An attempt was made to obtain the acid by oxidative fusion with sodium hydroxide in the presence of lead dioxide, but only α-naphthol was identified in the reaction mixture. Ultimately the more recent oxidative procedure described by Pearl (*J. Amer. Chem. Soc.*, 1946, **68**, 431) was adopted, and we now report the controlled oxidation of 4-hydroxynaphthaldehyde with silver oxide in excess of sodium hydroxide solution in conversions of up to 47% of the naphthoic acid, which has been characterised by the formation of the *O*-acetyl derivative. However, the product of this oxidation was difficult to purify and would appear to be contaminated by quinonoid materials.

There is no reference to the preparation of the esters from the parent acid, but Montmollin and Spieler (U.S.P. 1,474,928) synthesised the methyl and the ethyl ester of 4-hydroxynaphthoic acid directly from α-naphthol and carbon tetrachloride, sodium hydroxide, and the alcohol, in the presence of copper powder.

An indirect route to the alkyl 4-hydroxynaphthoates was therefore indicated. 4-Benzyloxynaphthaldehyde was oxidised to 4-benzyloxynaphthoic acid which, in turn, was esterified; hydrogenation of the benzyloxy-ester gave the required alkyl 4-hydroxynaphthoate.

The first step was best carried out by Pearl's procedure; oxidation with potassium permanganate in aqueous acetone was also investigated but this method invariably gave mixtures of the benzyloxynaphthoic acid and α-naphthol (presumably the latter arises from oxidation of the benzyl ether to the benzoyl ester, which is followed by hydrolysis to

the free hydroxynaphthoic acid and then decarboxylation). Esterification of sodium 4-benzyloxynaphthoate with the appropriate *n*-alkyl bromide or iodide required several days' reflux, and the reaction was only partly completed. Reduction of an alcoholic solution of the alkyl benzyloxynaphthoate with hydrogen and Raney nickel gave an almost quantitative yield of the alkyl 4-hydroxynaphthoate. These esters have a green alcoholic ferric reaction, less intense than that of 4-hydroxynaphthaldehyde.

Whilst the reduction of the esters proceeded smoothly, it has not proved possible to reduce the 4-benzyloxynaphthoic acid by the action of hydrogen with Raney nickel, or palladium–charcoal, in alcohol, ethyl acetate, or acetic acid. Thus the parent acid, which gave a red alcoholic ferric reaction and a chocolate precipitate in more concentrated solution (cf. Heller, *loc. cit.*), has so far only been obtained by direct oxidation of 4-hydroxynaphthaldehyde.

The biological activity of these compounds will be reported elsewhere.

Experimental

4-Hydroxynaphthaldehyde.—The aldehyde was prepared by the method of Gattermann and von Horlacher (*Ber.*, 1899, **32**, 285), as modified by Adams and Levine (*J. Amer. Chem. Soc.*, 1923, **45**, 2373), from α-naphthol with zinc cyanide and hydrogen chloride in dry ether. It was obtained as clusters of needles, m. p. 178—179°, from aqueous alcohol. Adams and Levine record m. p. 178°. The aldehyde gave a green alcoholic ferric reaction and was characterised by the formation of an *oxime*, which crystallised as needles, m. p. 140° (decomp.), from aqueous ethanol (Found: C, 70·7; H, 4·7; N, 7·7. $C_{11}H_9O_2N$ requires C, 70·6; H, 4·8; N, 7·5%). The *O*-acetyl derivative crystallised as long needles, m. p. 99°, from aqueous ethanol (Found: C, 72·7; H, 4·7. Calc. for $C_{13}H_{10}O_3$: C, 72·9; H, 4·7%). Kann *et al.* (*J. Amer. Chem. Soc.*, 1917, **39**, 1247) give m. p. 110°.

4-Hydroxynaphthoic Acid.—Silver oxide, prepared from silver nitrate (4·2 g.) and sodium hydroxide (1·0 g.), was suspended in water (25 ml.) and then treated with sodium hydroxide (5 g.). With continuous stirring 4-hydroxynaphthaldehyde (4·4 g.) was added and the temperature of the mixture was increased from 40° to 88—90° and kept there for 90 minutes. The silver was filtered off and washed with water (100 ml.), and the cooled filtrates were acidified with sulphur dioxide and then ether extracted. 4-Hydroxynaphthoic acid was separated from unchanged aldehyde by a sodium hydrogen carbonate extraction. Acidification of the extract with sulphur dioxide followed by ether extraction gave a yellow-reddish solution, which after evaporation at room temperature gave clusters of yellow needles in a red tar. 4-Hydroxynaphthoic acid (1·1 g.) was obtained as small buff needles, m. p. 180° (decomp.), from ethyl acetate–light petroleum (Found: C, 69·7; H, 4·3. Calc. for $C_{11}H_8O_3$: C, 70·2; H, 4·3%). Heller (*Ber.*, 1912, **45**, 675) gives m. p. 183—184°. 4-Hydroxynaphthaldehyde (2·3 g.) was recovered. The 4-hydroxynaphthoic acid was characterised as the *O*-acetyl derivative, crystallising as long needles, m. p. 179—180°, from aqueous ethanol (Found: C, 67·6; H, 4·3. Calc. for $C_{13}H_{10}O_4$: C, 67·8; H, 4·4%). Heller (*loc. cit.*) gives m. p. 178—179°. The acid gave a red alcoholic ferric reaction, and a chocolate precipitate in more concentrated solution.

4-Benzyloxynaphthaldehyde.—Sodium ethoxide [from sodium (3 g.) and ethanol (100 ml.)], 4-hydroxynaphthaldehyde (20 g.), and benzyl chloride (14·6 g.) were refluxed for 7 hours. The initial green colour slowly changed to brown during 5 hours. Filtration of the sodium chloride was followed by evaporation of the alcohol under reduced pressure and ether extraction. The washed and dried extract on vacuum distillation gave two fractions, benzyl ethyl ether (4·3 g.), b. p. 42°/3 mm., 185°/760 mm., and a yellow oil, b. p. 200—208°/0·3 mm. Trituration of the latter with light petroleum gave *4-benzyloxynaphthaldehyde* (9·4 g.) which crystallised as rectangular plates, m. p. 75°, from light petroleum (Found: C, 82·1; H, 5·4. $C_{18}H_{14}O_2$ requires C, 82·4; H, 5·4%). The aldehyde was characterised by the formation of an *oxime*, obtained as needles, m. p. 104°, from aqueous ethanol (Found: C, 77·8; H, 5·3; N, 5·2. $C_{18}H_{15}O_2N$ requires C, 78·0; H, 5·4; N, 5·0%).

4-Benzyloxynaphthoic Acid.—(*a*) Potassium permanganate (0·19 g.) in water (20 ml.) was added during 5 minutes to a boiling solution of 4-benzyloxynaphthaldehyde (0·65 g.) in acetone (50 ml.) and water (30 ml.). After 30 minutes' refluxing the hot solution was filtered and cooled; α-naphthol (0·35 g.), m. p. and mixed m. p. 90°, separated. Filtration and acidification with dilute hydrochloric acid gave crude 4-benzyloxynaphthoic acid (0·05 g.), m. p. 186°.

4-Benzyloxynaphthoic acid crystallised as plates, m. p. 194° [mixed m. p. with product (*b*) 194°], from ethyl acetate.

(*b*) Sodium hydroxide (2 g.) was added to silver oxide (1·2 g.) in water (10 ml.). At 55°, 4-benzyloxynaphthaldehyde (1·0 g.) was added, and the temperature of the mixture was increased to and kept at 80—90° for 30 minutes. The silver was filtered off and washed with water (50 ml.), and the combined filtrates were acidified with dilute hydrochloric acid. An ether extraction gave the crude *acid* (0·88 g.), m. p. 190°, which, when crystallised from ethyl acetate, formed long rectangular plates, m. p. 191—192° (Found : C, 77·6; H, 5·1. $C_{18}H_{14}O_3$ requires C, 77·7; H, 5·1%).

Methyl 4-Benzyloxynaphthoate.—Sodium (0·6 g.) was dissolved in absolute ethanol (100 ml.), and 4-benzyloxynaphthoic acid (2·8 g.) was added with shaking. Methyl iodide (4 g.) was added to the boiling mixture in three portions during 8 hours. After another 8 hours' refluxing the solution was filtered from sodium iodide, and the bulk of the solvent was removed under reduced pressure. The crude ester was extracted with ether, washed with 10% sodium hydroxide solution and then water, and dried. Evaporation of the ethereal solution gave a brown oil (2·1 g.) which solidified on cooling. A vacuum sublimation of the solid at 120—140°/4 × 10^{-3} mm. gave a sublimate, m. p. 61—62°. *Methyl 4-benzyloxynaphthoate* (1·42 g.) crystallised as rectangular plates, m. p. 59—60°, from light petroleum (Found : C, 77·9; H, 5·6. $C_{19}H_{16}O_3$ requires C, 78·0; H, 5·5%). 4-Benzyloxynaphthoic acid (0·4 g.) was recovered.

The following 4-benzyloxynaphthoates were similarly prepared (yields, given in parentheses, are from 2·8 g. of the acid and refer to the pure products; recovery refers to the quantity of unreacted acid recovered) : *ethyl* (1·2 g.; recovery, 0·9 g.), needles, m. p. 63—64° (Found : C, 78·2; H, 5·7. $C_{20}H_{18}O_3$ requires C, 78·3; H, 5·9%); n-*propyl* (1·3 g.; recovery, 0·9 g.), prisms, m. p. 67—68° (Found : C, 78·5; H, 6·2. $C_{21}H_{20}O_3$ requires C, 78·7; H, 6·3%), prepared in *n*-propanol; n-*butyl* (0·65 g.; recovery, 0·5 g.), needles, m. p. 51° (Found : C, 79·0; H, 6·6. $C_{22}H_{22}O_3$ requires C, 79·0; H, 6·6%); and n-*amyl* (1·0 g.; recovery, 1·2 g.), b. p. 242—246°/0·8 mm. (Found : C, 79·2; H, 7·0. $C_{23}H_{24}O_3$ requires C, 79·3; H, 6·9%).

Methyl 4-Hydroxynaphthoate.—Methyl 4-benzyloxynaphthoate (0·5 g.) in ethanol (30 ml.) was hydrogenated at room temperature and pressure, in the presence of Raney nickel. Hydrogen (55 ml.) was absorbed during 10 minutes, then, after filtration, the ethanol was removed under reduced pressure and the product crystallised from aqueous ethanol. Methyl 4-hydroxynaphthoate (0·3 g.) was isolated as plates, m. p. 167°, from petroleum–ethyl acetate (Found : C, 71·4; H, 5·1. Calc. for $C_{12}H_{10}O_3$: C, 71·3; H, 5·0%). Montmollin and Spieler (U.S.P. 1,474,928) give m. p. 178°. The ester gave a pale green alcoholic ferric reaction.

The following 4-hydroxynaphthoates were similarly prepared : ethyl (0·70 g.; from 1·1 g. of the 4-benzyloxy-compound), small plates, m. p. 136° (Found : C, 72·0; H, 5·6. Calc. for $C_{13}H_{12}O_3$: C, 72·2; H, 5·6%) (Montmollin and Spieler, *loc. cit.*, give m. p. 134°); n-*propyl* (0·62 g.; from 1·0 g.), plates, m. p. 110° (Found : C, 73·0; H, 6·0. $C_{14}H_{14}O_3$ requires C, 73·0; H, 6·1%); n-*butyl* (0·35 g.; from 0·65 g.), plates, m. p. 114° (Found : C, 73·7; H, 6·5. $C_{15}H_{16}O_3$ requires C, 73·7; H, 6·6%); n-*amyl* (0·35 g.; from 0·9 g.), plates, m. p. 100° (Found : C, 74·3; H, 7·0. $C_{16}H_{18}O_3$ requires C, 74·4; H, 7·0%). The last named gave a pale green reaction with alcoholic ferric chloride.

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697. *The Constitution of Mesquite Gum. Part IV.* Determination of the Structure of the Amide of 6-β-(4-Methyl D-Glucopyruronosyl) α-Methyl-D-galactopyranoside.*

By M. Abdel Akher, F. Smith, and D. Spriestersbach.

Controlled hydrolysis of mesquite gum was shown previously to give a monomethyl aldobiuronic acid (I) and 4-methyl D-glucuronic acid (Smith, *J.*, 1951, 2646). The crystalline amide (II) obtained from (I) is shown to be derived from 6-β-(4-methyl D-glucopyruronosyl) α-methyl-D-galactopyranoside.

Methanolysis of degraded mesquitic acid or the aldobiuronic acids obtained from it yielded 4-methyl methyl-D-glucopyruronoside methyl ester (White, *J. Amer. Chem. Soc.*, 1948, **70**, 367) and the methyl ester (II) of a monomethyl aldobiuronoside which was isolated as a crystalline amide (III). The determination of the structure of (III) forms the subject of this communication.

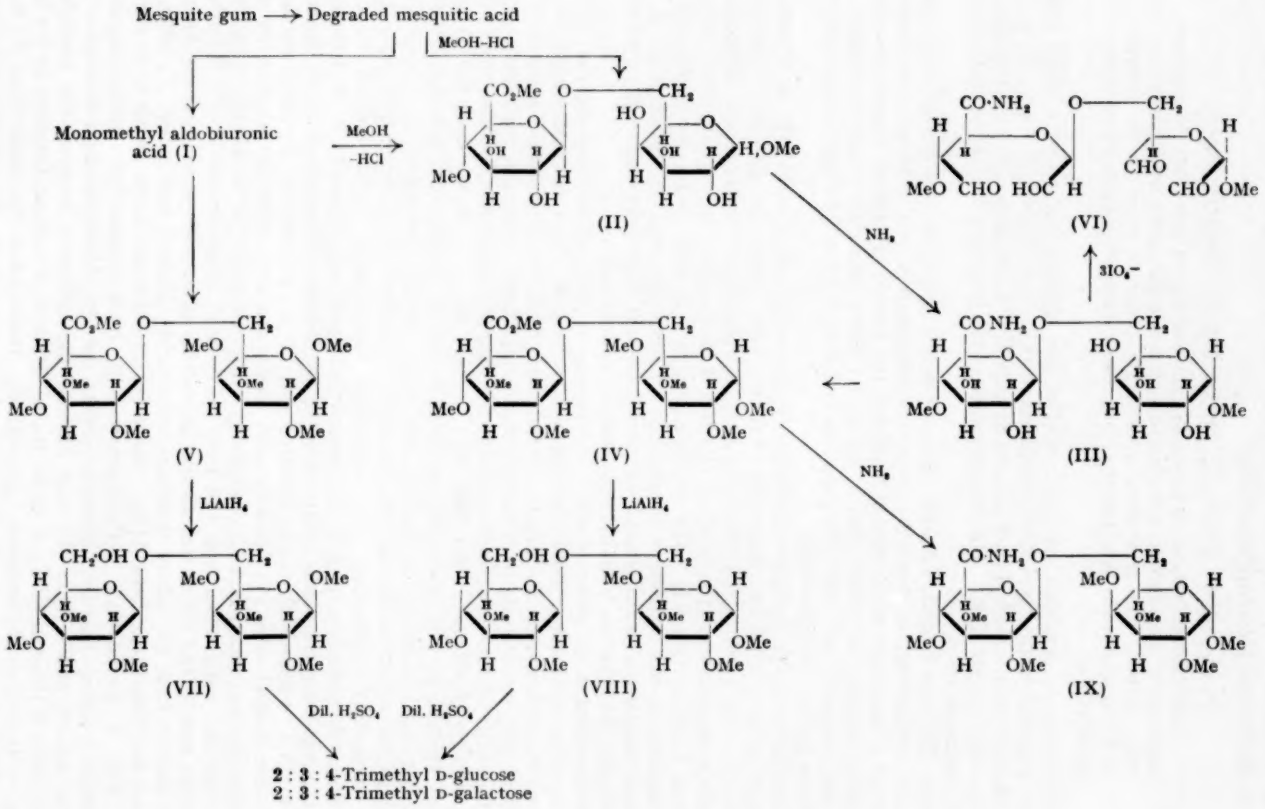
When (III) was hydrolysed with sulphuric acid it gave rise to 4-methyl D-glucuronic acid and D-galactose, as shown by paper chromatography, and prolonged methanolysis followed by treatment with ammonia yielded the known crystalline amide of 4-methyl α-methyl-D-glucopyruronoside (Smith, *loc. cit.*). There was thus reason to believe that (III) was composed of a unit of D-galactose and one of 4-methyl D-glucuronic acid, each unit being of the pyranose form.

Three molecular proportions of sodium periodate were consumed by (III) at 5°, with the liberation of one molecular proportion of formic acid. Since the 4-methyl D-glucuronic acid moiety is joined through its reducing group it is clear that it will consume one molecular proportion of periodate without the formation of formic acid, cleavage occurring between positions 2 and 3 (see VI). The methylgalactoside residue, being responsible for the consumption of two molecular proportions of periodate and the production of one molecular proportion of formic acid, was therefore most likely joined through position 6 to the reducing group of the 4-methyl D-glucuronic acid residue.

Confirmation of the presence of the 1 : 6-linkage in (III) was forthcoming from the fact that the fully methylated aldobiuronoside (IV), obtained either by methylation of (II) first with methyl sulphate and alkali and then with diazomethane or by treatment of the acid from (III) successively with diazomethane and Purdie's reagents, underwent smooth reduction with lithium aluminium hydride according to conditions previously used (Abdel Akher and Smith, *Nature*, 1950, **166**, 1037; Smith, *loc. cit.*; cf. Lythgoe and Trippett, *J.*, 1950, 1983) to give the crystalline methylglycoside of a hexamethyl disaccharide (VIII). The latter was recognized as 6-(2 : 3 : 4-trimethyl D-glucopyranosyl) 2 : 3 : 4-trimethyl methyl-D-galactopyranoside since on hydrolysis it yielded 2 : 3 : 4-trimethyl D-glucose and 2 : 3 : 4-trimethyl D-galactose. The crystalline disaccharide (VIII) differed from the crystalline disaccharide, 6-β-(2 : 3 : 4-trimethyl D-glucopyranosyl) 2 : 3 : 4-trimethyl β-methyl-D-galactopyranoside (VII), obtained by lithium aluminium hydride reduction of 6-β-(2 : 3 : 4-trimethyl D-glucopyruronosyl) 2 : 3 : 4-trimethyl β-methyl-D-galactopyranoside methyl ester (V) (Jackson and Smith, *loc. cit.*), although it gave the same hydrolysis products, namely, 2 : 3 : 4-trimethyl D-glucose and 2 : 3 : 4-trimethyl D-galactose.

It was also established that the fully methylated aldobiuronoside (IV) afforded a crystalline amide (IX) which was distinct in melting point and specific rotation from the amide derived from (V) whose structure was known (Jackson and Smith, *J.*, 1940, 74; Cunneen and Smith, *J.*, 1948, 1141). Since (VIII) has been shown above to be derived from 6-(2 : 3 : 4-trimethyl D-glucopyruronosyl) 2 : 3 : 4-trimethyl methyl-D-galactopyranoside it follows that the difference between the new aldobiuronamide derivative (IX) and the known amide from (V), and likewise the difference between the methylated disaccharides (VIII) and (VII), is to be traced either to the stereochemistry at the biose linkage or to that at the anomeric $C_{(1)}$ position. Inasmuch as the amide from (V) is the only 1 : 6-linked aldobiuronoside derivative obtained when the monomethyl aldobiuronic

* Part III, *J.*, 1951, 2646.


Mesquite gum
Degraded mesquitic acid
MeOH–HCl
Monomethyl aldobiuronic acid (I)
MeOH
–HCl
(II)
(III)
(IV)
(V)
(VI)
(VII)
(VIII)
(IX)
NH₃
NH₃
3IO₄⁻
LiAlH₄
LiAlH₄
Dil. H₂SO₄
Dil. H₂SO₄
2 : 3 : 4-Trimethyl D-glucose
2 : 3 : 4-Trimethyl D-galactose

acid (I) derived from mesquite gum is methylated directly with methyl sulphate and alkali and converted into an amide (Cunneen and Smith, *loc. cit.*), it is apparent that the two amides and the corresponding neutral disaccharides are derived from one and the same 1 : 6-β-linked aldobiuronic acid. The only difference between the amides and between the disaccharides must therefore lie in the position of the hydrogen and methoxyl groups at $C_{(1)}$. Since the amide from (V) and the stereochemically related disaccharide (VII) are β-glycosides it follows that (IX) and (VIII) must be α-methylglycosides. Consequently (III) is the amide of 6-β-(4-methyl D-glucopyruronosyl) α-methyl-D-galactopyranoside.

Experimental

Oxidation of the Amide (III) *of* 6-β-(4-*Methyl* D-*Glucopyruronosyl*) α-*Methyl*-D-*galactopyranoside with Sodium Periodate.*—The amide (III) (50·7 mg.; prepared according to Smith, *loc. cit.*) was dissolved in 0·083N-sodium periodate (50 ml.) and kept at 5° (see Abdel Akher and Smith, *J. Amer. Chem. Soc.*, 1951, **73**, 994). The rate of oxidation was followed by withdrawing portions (5 ml.) of the solution at suitable intervals and adding 0·01N-sodium arsenite (50 ml.), sodium hydrogen carbonate (1—2 g.), and a crystal of potassium iodide, and after 10 minutes back-titrating it with 0·01N-iodine, with the following results: 1·17 mols. (after 9 minutes); 1·58 (32 minutes); 1·89 (60 minutes); 2·11 (117 minutes); 2·41 (309 minutes); 2·98 (30 hours). After 68 hours and destruction of the excess of periodate with ethylene glycol (0·5 ml.), titration of an aliquot (5 ml.) of the solution with 0·01N-sodium hydroxide (indicator, methyl-red) showed that 1·1 mols. of formic acid were produced.

Hydrolysis of the Amide (III).—A solution of the amide (10 mg.) in N-sulphuric acid (0·5 ml.) in a small sealed tube was heated on the boiling-water bath for 18 hours, then neutralized with barium carbonate, filtered, passed through a column of " Dowex 50 " cation-exchange resin, and evaporated *in vacuo* to a syrup. This syrup, along with standard samples of D-galactose and 4-methyl D-glucuronic acid (prepared from the amide of 4-methyl methyl-D-glucopyruronoside by acid hydrolysis in the above manner), were subjected to partition chromatography on Whatman No. 1 filter paper with the upper layer of *n*-butanol–5N-formic acid (1 : 1) as the irrigating solvent. The syrup contained two components whose R_F values corresponded to D-galactose and 4-methyl D-glucuronic acid.

Treatment of the Amide (III) *with Methyl-alcoholic Hydrogen Chloride.*—The amide (15 mg.) was heated for 20 hours at 100° with 8·0% methanolic hydrogen chloride (2 ml.). The solution was neutralized with silver carbonate, filtered, and evaporated to dryness *in vacuo*. The product was transformed into the amide in the usual way with methanolic ammonia. On removal of the solvent, the amide of 4-methyl α-methyl-D-glucopyruronoside crystallized, m. p. 229—230° alone or on admixture with an authentic specimen (after crystallization from methanol).

Methylation of the Amide (III).—A solution of the amide (225 mg.) was methylated three times in the usual way at 40—50° with methyl sulphate (9 ml.) and 30% sodium hydroxide (24 ml.), the product being extracted with chloroform after each methylation. The syrupy product (195 mg.) was further methylated by the Purdie procedure and distilled, yielding 6-β-(2 : 3 : 4-trimethyl D-glucopyruronosyl) 2 : 3 : 4-trimethyl α-methyl-D-galactopyranoside methyl ester (IV) as a fairly mobile colourless liquid (0·158 g.), b. p. (bath-temp.) 196°/0·02 mm., n_D^{29} 1·4670, $[\alpha]_D^{23}$ +15·5° (*c*, 1·5 in methanol). The product did not crystallize when nucleated with 6-β-(2 : 3 : 4-trimethyl D-glucopyruronosyl) 2 : 3 : 4-trimethyl β-methyl-D-galactopyranoside methyl ester (V) which had m. p. 93°, $[\alpha]_D^{23}$ −40° (*c*, 1·2 in methanol) (Jackson and Smith, *loc. cit.*).

The Amide (IX) *of* 6-β-(2 : 3 : 4-*Trimethyl* D-*Glucopyruronosyl*) 2 : 3 : 4-*Trimethyl* α-*Methyl*-D-*galactopyranoside.*—A solution of the methylated aldobiuronoside (IV) (120 mg.) in methanol (4 ml.) was cooled to 0°, saturated with ammonia, and kept for 12 hours at 5° and for 5 hours at 25°. Removal of the solvent *in vacuo* yielded the crystalline *amide* (IX) of 6-β-(2 : 3 : 4-trimethyl D-glucopyruronosyl) 2 : 3 : 4-trimethyl α-methyl-D-galactopyranoside, which crystallized from ethanol–ether as needles, m. p. 160°, $[\alpha]_D^{23}$ +40·5° (*c*, 0·65 in water) (Found: OMe, 48·1. $C_{19}H_{35}O_{11}N$ requires OMe, 47·9%).

6-β-(2 : 3 : 4-*Trimethyl* D-*Glucopyranosyl*) 2 : 3 : 4-*Trimethyl* α-*Methyl*-D-*galactopyranoside* (VIII).—(i) *The methyl ester* (IV) *of* 6-β-(2 : 3 : 4-*trimethyl* D-*glucopyruronosyl*) 2 : 3 : 4-*trimethyl* α-*methyl*-D-*galactopyranoside.* (*a*) A solution of the amide (III) of 6-β-(4-methyl D-glucopyruronosyl) α-methyl-D-galactopyranoside (198 mg.) in 0·1N-sodium hydroxide (10 ml.) was heated at 50—60° until all ammonia was evolved (litmus). The solution was treated with

0·1N-sulphuric acid (9·9 ml.) and evaporated to dryness *in vacuo*. The product was extracted with methanol, treated with a slight excess of ethereal diazomethane and, after removal of solvent, subjected to three treatments with Purdie's reagents in the usual way. A small amount of methanol was used in the first treatment to increase the solubility of the methyl ester. Distillation of the product yielded the *methyl* ester (IV) of 6-β-(2 : 3 : 4-trimethyl D-glucopyruronosyl) 2 : 3 : 4-trimethyl α-methyl-D-galactopyranoside, b. p. (bath-temp.) 210°/0·01 mm., n_D^{20} 1·4670, $[\alpha]_D^{20}$ +17·5° (*c*, 2·4 in methanol) (Found: OMe, 50·8. $C_{20}H_{36}O_{12}$ requires OMe, 52·9%).

(*b*) A solution of the fully methylated aldobionamide (IX) (20 mg.) in N-sodium hydroxide (5 ml.) was warmed at 50—60° and nitrogen was passed through the solution until no more ammonia was evolved (litmus). The solution was acidified with N-sulphuric acid (5·5 ml.), and the product extracted repeatedly with chloroform. The chloroform extract was dried ($MgSO_4$), filtered, and concentrated to a syrup. The latter was dissolved in ether (10 ml.) and esterified by treatment with a slight excess of ethereal diazomethane (persistent yellow colour). Removal of the solvent gave the methyl ester of 6-β-(2 : 3 : 4-trimethyl D-glucopyruronosyl) 2 : 3 : 4-trimethyl α-methyl-D-galactopyranoside (IV) as above.

(ii) *Reduction of* 6-β-(2 : 3 : 4-*trimethyl* D-*glucopyruronosyl*) 2 : 3 : 4-*trimethyl* α-*methyl*-D-*galactopyranoside methyl ester* (IV) *with lithium aluminium hydride*. A solution of the methyl ester (IV), obtained as in (*b*) above, in ether (5 ml.), was added dropwise with stirring to a solution of lithium aluminium hydride (0·3 g.) in ether (10 ml.). The reaction mixture was kept at 25° for 10 hours, refluxed for 4 hours, cooled, poured into water (50 ml.), acidified with dilute hydrochloric acid, and extracted three times with chloroform. The combined chloroform extract was dried (Na_2SO_4) and concentrated *in vacuo*. The syrup crystallized spontaneously, yielding 6-β-(2 : 3 : 4-*trimethyl* D-*glucopyranosyl*) 2 : 3 : 4-*trimethyl* α-*methyl*-D-*galactopyranoside* (VIII), needles (from ether–light petroleum), m. p. 114—115°, $[\alpha]_D^{24}$ +50° (*c*, 0·5 in water) (Found: C, 51·7; H, 8·2. $C_{19}H_{36}O_{11}$ requires C, 51·8; H, 8·2%).

Hydrolysis of 6-β-(2 : 3 : 4-*Trimethyl* D-*Glucopyranosyl*) 2 : 3 : 4-*Trimethyl* α-*Methyl*-D-*galactopyranoside* (VIII).—A solution of the methylated disaccharide (VIII) (16·5 mg.) in N-sulphuric acid (1 ml.) was heated in a sealed tube for 20 hours on a boiling-water bath. The hydrolysate was diluted with water and neutralized by passage through a column of "Duolite A-4" anion-exchange resin. Evaporation of the solution to dryness *in vacuo* gave a neutral syrup. A small portion of the syrup was chromatographed on Whatman No. 1 filter paper with ethyl methyl ketone–water azeotrope as the irrigating solvent. After about 1 hour the paper was dried in the air for about 30 minutes, sprayed with the *NN*¹-dimethyl-*p*-phenylenediamine hydrochloride reagent (see Boggs *et al.*, *Nature*, 1951, **166**, 520) and heated for about 5 minutes at 130°. Two well-defined spots appeared, with R_F 0·65 and 0·42 respectively, and corresponded exactly with spots produced on the same chromatogram by authentic specimens of 2 : 3 : 4-trimethyl D-glucose and 2 : 3 : 4-trimethyl D-galactose respectively. The rest of the mixture was treated with aniline (20 mg.) in boiling ethanol (1 ml.) for 3 hours. Removal of the excess of the solvent *in vacuo* yielded crystalline 2 : 3 : 4-trimethyl D-galactose anilide as rhombic plates, m. p. 164° not depressed on admixture with an authentic specimen.

Reduction of the Methyl Ester (V) *with Lithium Aluminium Hydride*.—A solution of the ester (V) (Jackson and Smith, *loc. cit.*) (173 mg.) in dry ether (10 ml.) was added slowly to a solution of lithium aluminium hydride (500 mg.) in ether (20 ml.) (see Smith, *loc. cit.*). After 30 minutes at room temperature the solution gave a negative hydroxamic acid test for esters (see Abdel Akher and Smith, *J. Amer. Chem. Soc.*, 1951, **73**, 5859). The reaction mixture was poured into water, and the aqueous phase extracted repeatedly with ether. The combined extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. Crystallization occurred spontaneously, yielding 6-β-(2 : 3 : 4-*trimethyl* D-*glucopyranosyl*) 2 : 3 : 4-*trimethyl* β-*methyl*-D-*galactopyranoside* (VII), m. p. 145·5°, $[\alpha]_D^{25}$ −39° (*c*, 3·9 in chloroform) (after recrystallization from ether–light petroleum) (Found: C, 51·84; H, 8·34. $C_{19}H_{36}O_{11}$ requires C, 51·8; H, 8·3%). Saponification for 2 hours with 0·1N-sodium hydroxide was without effect on (VII).

A solution of the above methylated disaccharide (VII) (10 mg.) in N-sulphuric acid (1 ml.) was heated for 6 hours in a boiling-water bath. The solution was cooled, neutralized with "Duolite A-4" anion-exchange resin, and concentrated *in vacuo* to a syrup. Paper-chromatographic analysis, with ethyl methyl ketone–water azeotrope as the irrigating solvent, revealed the presence of two components which corresponded to 2 : 3 : 4-trimethyl D-glucose (R_F 0·61) and 2 : 3 : 4-trimethyl D-galactose (R_F 0·40).

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698. *The Action of Crystalline β-Amylase on Some Glycogens.*

By D. J. Bell and D. J. Manners.

Glycogens (chain-length *ca.* twelve radicals) on β-amylolysis with the crystalline sweet-potato enzyme lose *ca.* 45% of their exterior chains solely as maltose. Available evidence points to an irregularly branched structure for glycogens; on the average, exterior chains contain *ca.* 7 glucose radicals, and interior chains *ca.* 4. The positions of branching points in the unit chains of amylopectins and 18-radical glycogens are discussed.

By potassium periodate oxidation, chain lengths of thirteen units were found for cat-liver and fœtal-sheep-liver glycogens. Three samples of glycogen from *Mytilus edulis* had different chain lengths (*ca.* 5, 12, and 17). A sample of *Helix pomatia* glycogen had a chain length of *ca.* 7 (cf. Baldwin and Bell, *Biochem. J.*, 1940, **34**, 139). These very short-chain glycogens gave no evidence of being degraded.

The approximate position of the branching points in the constituent unit chains of polysaccharides of the amylopectin–glycogen type can be assessed by studying the action thereon of purified β-amylase. β-Amylase attacks only the exterior chains of 1 : 4-α-linked glucose radicals, and by the stepwise hydrolysis of alternate glucosidic links liberates maltose. Hydrolysis starts at the non-reducing end of the exterior chain and continues until an obstruction is encountered; this appears to be the inter-chain 1 : 6-linkage. The products of the β-amylolysis of these branched polysaccharides are therefore maltose and a dextrin of high molecular weight with outer chain "stubs" consisting of perhaps one or two glucose radicals and still retaining intact the original inter-chain linkages (cf. Bernfeld, *Adv. Enzymology*, 1951, **12**, 379; Hanes, *New Phytologist*, 1937, **36**, 101, 189; Myrbäck and Neumüller, "The Enzymes," New York, 1950, Vol. I, Part 1, p. 653; Peat, *Adv. Enzymology*, 1951, **11**, 339). An accurate determination of the maltose produced by β-amylolysis is therefore a measure of the exterior chain length.

Few studies of the action on glycogens (unit chain length often undetermined) of non-crystalline, and almost certainly mixed, enzyme preparations having β-amylolytic activity have so far been reported. Table 1 emphasises the state of present knowledge, only seven out of 16 specimens having been analysed for chain length.

Table 1. *The β-amylolysis of some glycogens (non-crystalline β-amylases).*

Source of glycogen	Unit chain length * A	Unit chain length * B	Source of β-amylase	Conversion into maltose, %	Ref.
Beef liver (Hoffmann–La Roche)	—	—	Wheat	45	*a*
Mussel (Merck)	—	—	Wheat	45	*a*
Mussel (Merck)	11	—	Wheat	47	*b*
Mussel, fraction I †	—	—	Wheat	43	*c*
,, II	—	—	Wheat	33	*c*
,, III	—	—	Wheat	31	*c*
Hoffmann–La Roche	—	—	Wheat	46	*c*
Hoffmann–La Roche	—	11	Barley	38—46	*d*
Corn (Golden Bantam)	11	—	Wheat	20	*e*
Rabbit liver	—	—	Wheat	45	*e*
Corn (Golden Bantam)	—	10	Wheat	48	*f*
Yeast, fraction I †	—	—	Wheat	47	*g*
,, II	—	—	Wheat	45	*g*
Yeast	—	12	Barley	50	*h*
Rabbit liver	—	12	Barley	43	*h*
Rabbit liver	18	—	Wheat	53	*i*

* A, By methylation. B, By periodate oxidation. † Fractionation by electrodialysis.

[a] Meyer and Press, *Helv. Chim. Acta*, 1941, **24**, 58. [b] Meyer and Fuld, *ibid.*, 1941, **24**, 375. [c] Meyer and Jeanloz, *ibid.*, 1943, **26**, 1784. [d] Carlquist, *Acta Chem. Scand.*, 1948, **2**, 770. [e] Morris, *J. Biol. Chem.*, 1944, **154**, 503. [f] Meyer and Fuld, *Helv. Chim. Acta*, 1949, **32**, 757. [g] Jeanloz, *ibid.*, 1944, **27**, 1501. [h] Northcote, *Biochem. J.*, 1952, in the press. [i] Halsall, Hirst, Hough, and Jones, *J.*, 1949, 3200.

In our work we used only samples of glycogen prepared by ourselves. Commercially derived preparations may be of uncertain origin, chemically degraded, and even more heterogeneous than average laboratory products (cf. Putzeys and Verhoeven, *Proc. Int. Colloquium Macromol., Amsterdam*, 1949, 267; Kerr, Katzbeck, and Cleveland, *J. Amer. Chem. Soc.*, 1951, **73**, 111). Through the kindness of Professor C. S. Hanes, F.R.S., we were provided with a sample of crystalline sweet-potato β-amylase prepared by Professor A. K. Balls (Balls, Thompson, and Walden, *J. Biol. Chem.*, 1946, **163**, 571; 1948, **173**, 9). The enzyme was free from maltose and α-amylase, and had no Z-enzyme activity (cf. Peat, Pirt, and Whelan, *J.*, 1952, 705) as judged by its inability to hydrolyse soluble laminarin or yeast glucan or to hydrolyse potato amylose to more that 76%. One of us has recently found (Manners, 1952, Thesis, Cambridge) that non-crystalline barley β-amylase preparations, although free from maltase and α-amylase, contain sufficient of a β-glucosidase to attack not only insoluble yeast glucan and soluble laminarin (cf. Peat, Thomas, and Whelan, *J.*, 1952, 722; Dillon and O'Colla, *Nature*, 1950, **166**, 67; *Chem. and Ind.*, 1951, 111), but also to remove the barriers in potato amylose preventing complete β-amylolysis.

We have examined the action of Ball's crystalline β-amylase on liver and muscle glycogens from various mammals, and on certain invertebrate glycogens. Our results, when enzymic action had been carried to completion, are summarised in Table 2 [a preliminary account of these results has recently been given by one of us (Manners, *Biochem. J.*, 1952, **51**, xxx)].

TABLE 2. *The β-amylolysis of some glycogens (crystalline β-amylase).*

Source of glycogen	Unit chain length * A	B	conversion into maltose (%)	Approx. exterior chain length
Rabbit liver	12[a]	13	43	7
Foetal-sheep liver	—	13	49	8
Cat liver	—	13	48	8
Rabbit muscle	11[a]	13	45	7
Horse muscle	12[b]	11	42	6
Human muscle	—	12	41	6—7
Mytilus edulis, I	—	12	43	6—7
,, II	18[c]	16	47	9—10
,, III	—	*ca.* 5	41	3
Ascaris lumbricoides	13—14[d]	12	49	7
Helix pomatia	—	*ca.* 7	37	4

* See footnote to Table 1.

[a] Bell, *J.*, 1948, 992. [b] Bell, *Biochem. J.*, 1937, **31**, 1683. [c] *Idem, ibid.*, 1936, **30**, 2144. [d] Baldwin and King, *ibid.*, 1942, **36**, 37.

When no further reducing sugar was liberated in each experiment, suitable examination of the digests showed that the β-amylase was still active. In certain experiments, further addition of enzyme failed to increase the β-amylolysis limit. The values in Table 2 therefore represent true β-amylolysis limits. Paper chromatography (Hough, Jones, and Wadman, *J.*, 1950, 1702) showed maltose to be the only sugar present. The absence of D-glucose was confirmed by manometrical treatment of final digests with glucose oxidase (cf. Keilin and Hartree, *Biochem. J.*, 1948, **42**, 230), no oxygen uptake being observed.

We determined the unit chain lengths of the glycogens essentially by potassium periodate oxidation at room temperature (Halsall, Hirst, and Jones, *J.*, 1947, 1399). Halsall *et al.* calculated unit chain lengths from formic acid titrated after 150 hours, this being the time taken for the similar production of 1 mol. of formic acid from β-methylmaltoside (Halsall, Hirst, and Jones, *J.*, 1947, 1429). In our experience, a 150-hour titre gives incorrect values for unit chain lengths; we have therefore allowed oxidation to proceed until a maximum constant formic acid concentration is reached (Table 3). Under these conditions, the final formic acid concentration is *ca.* 0·0025N and is not affected by the excess of periodate (cf. Sarkar, *Nature*, 1951, **168**, 122). We find no evidence of "over-oxidation"; no free iodine appeared in the reaction media. Our results agree closely with those obtained by methylation end-group assay of the *same* samples (Table 2).

Our experiments show that β-amylolysis of a 12-radical glycogen converts *ca.* 45% of the molecule into maltose, leaving unattacked a β-limit-dextrin of chain length *ca.* 6·5. Since

the exterior chain " stubs " of this dextrin contain *ca.* 1·5 glucose radicals (Meyer, *Adv. Enzymology*, 1943, **3**, 109) it follows that (*a*) the glycogen has an exterior chain length of *ca.* 7 glucose radicals, (*b*) the average position of the inter-chain branch point is at the 8th glucose radical from the non-reducing end, and (*c*) the average interior chain length must be *ca.* 4 radicals.

As already noted, β-amylolysis is considered to shorten exterior chains of glycogen by hydrolytic removal of maltose radicals. From the results in Table 2, we observed that, in some instances, β-amylolysis results in the loss of an odd or a fractional number of glucose radicals—wholly, however, in the form of maltose. These numbers must represent the average of the loss of an even number of glucose radicals from individual unit chains, thus indicating a variable exterior chain length, and hence an irregularly branched structure. Other available evidence points to an irregularly branched structure for glycogen (cf. Meyer, *loc. cit.*). Bell and Manners (*Biochem J.*, 1951, **49**, lxxvii) have shown that barley α-amylase will hydrolyse some (but not all) of the interior chains of rabbit-liver glycogen. The residual dextrins so obtained can be hydrolysed further by barley β-amylase. The hydrolysis of an interior chain is assumed to occur at about the mid-point (Myrbäck, *Arkiv Kemi*, 1950, **2**, 417), and since some interior chains thus ruptured are susceptible to further β-amylolysis the fragments must contain at least 3—4 glucose radicals. The original glycogen must therefore contain some interior chains of 6—8 glucose radicals, despite our observed mean interior chain length of *ca.* 4. Swanson and Cori (*J. Biol. Chem.*, 1948, **172**, 815), after a study of the " activation " of phosphorylase by glycogen α-dextrins, suggested that some of the interior chains of glycogen must contain *ca.* 6—8 glucose radicals. Swanson (*J. Biol. Chem.*, **172**, 825), from a study of their iodine complexes, suggested that glycogen β-limit-dextrins, too, contain some interior chains of *ca.* 8 glucose radicals. Meyer and Fuld (*Helv. Chim. Acta*, 1941, **24**, 375) found that mussel glycogen of chain length 11 contained interior chains of an average length of 3 glucose radicals. From Table 2 it can be seen that eight different samples of 12-unit glycogen have an average interior chain length of *ca.* 4 glucose radicals. It therefore seems likely that the interior structure of glycogen is irregular, and that glycogen should be considered as a macromolecule built up of several thousand unit chains, of varied chain length—the average of which is normally 12—which are randomly linked together by means of 1 : 6-glucosidic linkages. We do not propose to comment, at the moment, on the existence of glycogens with unit chains of *ca.* 6 or 18 glucose radicals (cf. Abdel-Akher and Smith, *J. Amer. Chem. Soc.*, 1951, **73**, 994). We have noted, however, that the glycogens from *Helix pomatia* and *Mytilus edulis* III had a negligible reducing power, and that the former gave an opalescent solution, which is indicative of high molecular weight (cf. Harrap and Manners, *Nature*, 1952, in the press. It is concluded that these invertebrate glycogens are the native polysaccharides, and not artefacts produced by degradation during their isolation.

β-Amylolysis of amylopectins has been studied by several groups of workers, *e.g.*, K. H. Meyer *et al.*, Myrbäck *et al.*, and Haworth *et al.*, and the results obtained have been reviewed by Myrbäck (*loc. cit.*), Bell (*Ann. Reports*, 1947, **44**, 217) and Bernfeld (*loc. cit.*). They show that 50—62% conversion of the polysaccharide into maltose takes place, which indicates that the mean situation of the branch point of a 25-radical amylopectin is at *ca.* the 17th glucose radical from the non-reducing end, and that the ratio of the exterior chain length to the interior chain length is 16 : 8. We find that the ratio of the exterior to interior chain lengths of a 12-unit glycogen is also *ca.* 2 : 1. Glycogens therefore differ from amylopectins mainly in the length of their unit chains, and not in the *relative* position of their branch points, even though β-amylolysis removes a relatively greater part of amylopectin (*ca.* 55%) than of glycogen (*ca.* 45%). The latter fact presumably arises from the mode of synthesis of these branched polysaccharides, the P- and Q-enzymes in plants having catalytic properties almost identical with those of the phosphorylase and the branching of animal tissues.

It is interesting to compare our results on the β-amylolysis of 12-radical glycogens with that of Halsall, Hirst, Hough, and Jones (*J.*, 1949, 3200) who found that a sample of rabbit-liver glycogen (chain length 18) gave a 53% conversion into maltose.

The exterior chain length of this polysaccharide is therefore *ca.* 11, and the interior chain length *ca.* 6, pointing to a structure intermediate between amylopectin and a typical 12-radical glycogen.

Experimental

Preparation of Glycogens.—The glycogens, isolated from the appropriate tissue by the "Pflüger technique" or by hot aqueous extraction, were purified by precipitation with acetic acid (Bell and Young, *Biochem. J.*, 1934, **28**, 882) and dried at 100° over phosphoric oxide for 3—4 hours in a high vacuum.

Crystalline β-Amylase Solution.—A stock solution (*ca.* 20 mg. in 20 ml. of water) was stored at 0° and diluted as required.

Determination of Reducing Sugar.—Reducing sugar (maltose) was determined by the Shaffer–Somogyi reagent 60 (*J. Biol. Chem.*, 1933, **100**, 695) as modified by Hanes and Cattle (*Proc. Roy. Soc.*, 1938, *B*, **125**, 387). The reagent, calibrated against maltose, would determine 0·5—4·0 mg. of maltose in 5 ml. of aqueous samples, provided the time of heating (15 minutes) was strictly adhered to.

Precautions against Mould Contamination.—Toluene, as used by Halsall *et al.* (*loc. cit.*) with crystalline β-amylase, was found to denature some of the enzyme. A concentration of 0·1—0·2% of propionate (cf. Crook, Carpenter, and Klens, *Science*, 1950, **112**, 656) prevented mould contamination during enzymic digestion.

Preliminary Experiments (at 28°).—(a) *Reducing power of the enzyme.* A digest was set up containing β-amylase solution (1 ml.) distilled water (7 ml.), and 0·2M-acetate buffer of pH 4·6 (5 ml.). Aliquot portions (4 ml.) of the digest were analysed for reducing power:

Time of incubation (hrs.)	0	70
Ml. of 0·01N-$Na_2S_2O_3$	0·04	0·02

i.e., the enzyme itself has a negligible reducing power.

(b) *Maltase activity.* A digest was set up containing maltose (15·6 mg.), 0·2M-acetate buffer of pH 4·6 (9 ml.), distilled water (20 ml.), 9% sodium propionate solution (0·5 ml.), and β-amylase solution (0·5 ml.). Aliquot portions (4 ml.) were analysed:

Time of incubation (hrs.)	0	47	200
Ml. of 0·01N-$Na_2S_2O_3$	3·65	3·60	3·57

i.e., the enzyme has no maltase activity.

(c) *α-Amylase activity.* A digest was set up containing 1% starch solution (2 ml.), 0·2M-acetate buffer of pH 4·6 (9 ml.), and distilled water (22 ml.). A sample (4 ml.) was withdrawn for determination of the reducing power of the starch. β-Amylase solution (1 ml.) was added, and aliquot portions (4 ml.) of the digest were analysed at intervals for maltose:

Time of incubation (hrs.)	0·16	0·5	1·67	24	46
Maltose found (mg.)	12·3	12·5	12·5	12·5	12·4

The constancy of the reducing power of the digest shows the absence of α-amylase in the β-amylase preparation.

(d) *Z-Enzyme activity.* Digests were set up containing yeast glucan (37·7 mg.) or soluble laminarin (35·9 mg.), distilled water (6 ml.), 0·2M-acetate buffer of pH 4·6 (5 ml.), and β-amylase solution (1 ml.). Aliquot portions (5 ml.) were analysed:

Time of incubation (hrs.)	Glucan digest	Laminarin digest
	Ml. of 0·01N-$Na_2S_2O_3$	
0	0·41	0·05
70	0·50	0·22

The slight increases in reducing power correspond to a hydrolysis of the glucan of *ca.* 0·14% and of the laminarin of *ca.* 0·3%.

The action of β-amylase on potato amylose was also studied as follows: the digest contained amylose solution (2·21 mg./ml.; 10 ml.), 0·2M-acetate buffer of pH 4·6 (5 ml.), distilled water (19 ml.), 9% sodium propionate solution (0·5 ml.), and β-amylase solution (0·5 ml.). The

amylose concentration was determined by Pirt and Whelan's method (*J. Sci. Food Agric.*, 1951, **5**, 224). The course of hydrolysis was as follows:

Time of incubation (hrs.)	17	41	335
% Conversion to maltose	69·5	71·2	75·6

In the presence of Z-enzyme, β-amylase hydrolysis of amylose was almost complete (Peat, Thomas, and Whelan, *J.*, 1952, 722).

Main Experiments.—Enzymic digests were set up containing glycogen (30—60 mg.), 0·2M-acetate buffer of pH 4·6 (5—1 ml.), distilled water (10—25 ml.), 9% sodium propionate solution (0·5—1·0 ml.). A sample (usually 3 ml.) was removed for the determination of the reducing power of the glycogen. β-Amylase solution (1 ml.) was then added. Samples were analysed, at intervals, for maltose, after incubation at 28°. The final β-amylolysis limits so obtained are recorded in Table 2 (mean of duplicate experiments which agreed within ±1%). When a constant maximum titre has been obtained, one drop of each digest was added to 2 ml. of 1% starch solution. The presence of active enzyme was shown by the formation of reducing sugar, controls being carried out with 1 drop of each digest in 1 ml. of water. In some experiments a second portion of β-amylase solution was added, after β-amylolysis has proceeded for 22 hours, but without increase in the β-amylolysis limit.

Examination of the β-Amylolytic Digests for D-*Glucose.*—(a) *Paper chromatography.* Samples of the digests were examined on paper chromatograms (Hough, Jones, and Wadman, *J.*, 1950, 1702), aniline phthalate being used as the developing agent. In all instances, maltose alone was detected.

(b) *Glucose oxidase.* Aliquots (3 ml.) of the digests were treated with glucose oxidase (cf. Keilin and Hartree, *Biochem. J.*, 1948, **42**, 230) in the presence of azide (Monod, personal communication). No oxygen uptake was observed. A control experiment, using 1·58 mg. of glucose, gave an oxygen uptake of 195 μl., equivalent to 123 μl./mg. of glucose (theory, 124·4 μl./mg. of glucose). Thus the only reducing sugar present in the β-amylolytic digests was maltose, and hence, the determination of the increase in reducing power (as maltose) of an aliquot portion of the digest was a true measure of the extent of β-amylolysis.

Potassium Periodate Oxidation of Glycogens.—The oxidations (Halsall, Hirst, and Jones, *J.*, 1947, 1399) were carried out at 15—20° in brown bottles (cf. Head, *Nature*, 1950, **165**, 236), on rotating rollers. Aliquots, after addition of ethylene glycol, were titrated against 0·01M-sodium hydroxide, in a stream of carbon dioxide-free air (methyl-red).

Preliminary experiments on muscle glycogens from horse, man, and rabbit showed that production of formic acid continued after 150 hours (Table 3). The unit chain lengths, in glucose radicals, calculated from the 150-hr. titre were: horse muscle glycogen, 16; rabbit muscle glycogen, 17; and human muscle glycogen, 15.

TABLE 3. *Oxidation of muscle glycogens by saturated potassium periodate solution.*

Time (hrs.)	Formic acid production (mg.) Human (414·8 mg.)	Rabbit (411·7 mg.)	Horse (684·4 mg.)	Time (hrs.)	Formic acid production (mg.) Human (414·8 mg.)	Rabbit (411·7 mg.)	Horse (684·4 mg.)
64	4·1	3·0	6·8	166	8·4	6·8	13·4
93	6·0	4·9	9·4	208	9·6	8·1	15·1
138	7·4	5·5	11·8	256	10·5	8·5	15·9
150	7·9	6·6	12·4	332	10·5	8·6	16·0

The method of Halsall *et al.* (*loc. cit.*) was therefore modified in the present study, in that the unit chain length was calculated from the maximum formic acid titre (after *ca.* 300 hours). The results so obtained are summarised in Table 2.

We thank Professor C. S. Hanes, F.R.S., for the gift of crystalline β-amylase. One of us (D. J. M.) gratefully acknowledges the award of a Research Studentship from the Agricultural Research Council, and also a Special Grant which enabled him to spend several weeks at the Institut Pasteur, Paris.

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699. *Steroids. Part IV.* Stigmasta-7 : 9(11) : 22-trien-3β-yl Acetate.*

By J. A. McEwan and F. S. Spring.

22 : 23-Dibromostigmasta-7 : 9(11)-dien-3β-yl acetate and stigmasta-7 : 9(11) : 22-trien-3β-yl acetate have been obtained from α-spinasteryl acetate.

The nuclear ethylenic linkage of α-spinasterol was shown to be located between $C_{(7)}$ and $C_{(8)}$ by Barton and Cox (*J.*, 1948, 1354; Barton *J.*, 1945, 813). Fieser, Fieser, and Chakravarti (*J. Amer. Chem. Soc.*, 1949, **71**, 2226) confirmed the structure of α-spinasterol as stigmasta-7 : 22-dien-3β-ol by its partial synthesis from stigmasterol. An efficient method for the conversion of α-dihydroergosterol (ergosta-7 : 22-dien-3β-ol) into ergosterol-D [ergosta-7 : 9(11) : 22-trien-3β-ol] has recently been described (Anderson, Stevenson, and Spring, *J.*, 1952, 2901). The present communication describes the application of this method to the analogously constituted α-spinasterol.

Treatment of α-spinasteryl acetate with bromine gives a tetrabromostigmastenyl acetate in poor yield. Partial debromination of the tetrabromo-derivative by using sodium iodide yields 22 : 33-dibromostigmasta-7 : 9(11)-dien-3β-yl acetate which exhibits the characteristic ultra-violet absorption spectrum of 7 : 9(11)-dienic steroids. Debromination of the dibromo-derivative with zinc gives stigmasta-7 : 9(11) : 22-trien-3β-yl acetate which is also obtained by oxidation of α-spinasteryl acetate with mercuric acetate. The most efficient method for the preparation of stigmasta-7 : 9(11) : 22-trien-3β-yl acetate from α-spinasteryl acetate is by treatment with bromine at a low temperature followed by direct debromination of the reaction product with zinc dust.

Experimental

M.p.s are uncorrected. Specific rotations were measured in chloroform, except where otherwise stated, a 1-dm. tube being used at approximately 15°. Ultra-violet absorption spectra were measured in ethanol with a Unicam SP. 500 spectrophotometer. Grade II alumina was used for chromatography.

α-Spinasteryl Acetate.—An extract from lucerne was supplied to us by Dr. W. Mitchell of Stafford Allen and Sons, Ltd., to whom we express our thanks. The non-saponifiable matter (105 g.) from lucerne, in benzene (2 l.), was chromatographed on alumina (50 × 6 cm.). The fractions eluted with benzene (7·5 l.), benzene–ether (9 : 1; 1 l.), benzene–ether (7 : 3, 1 l.), benzene–ether (1 : 1, 3 l.), and benzene–methanol (199 : 1, 3 l.) were discarded. Continued elution with benzene–methanol (199 : 1, 8 l.) gave a brown wax (approx. 50 g.). A solution of this wax in pyridine (200 c.c.) and acetic anhydride (40 c.c.) was kept at room temperature; after 18 hours the separated crystalline solid (8 g.) was collected and recrystallised from methanol–chloroform, giving α-spinasteryl acetate (2·7 g.) as plates, m. p. 182—185°, $[\alpha]_D$ −3·5°, −5° (*c*, 2·0, 1·9) (Found: C, 82·0; H, 11·4. Calc. for $C_{31}H_{50}O_2$: C, 81·9; H, 11·1%). A solution of the solid obtained from the acetic anhydride–pyridine mother liquors, by precipitation with water, in benzene (1 l.) was chromatographed on alumina (50 × 6 cm.), and the column was washed with benzene (2 l.). The solid (12 g.) obtained by evaporation of the benzene filtrate was crystallised from chloroform–methanol to give α-spinasteryl acetate (2·8 g.), m. p. 177—180°, $[\alpha]_D$ −3° (*c*, 2·5). Hydrolysis of α-spinasteryl acetate gave α-spinasterol as plates, m. p. 167—169°, $[\alpha]_D$ −2°, −1° (*c*, 0·8, 2·0).

Tetrabromostigmastenyl Acetate.—A solution of α-spinasteryl acetate (500 mg.) in dry ether (35 c.c.) was treated at 0° with a solution of bromine in glacial acetic acid (10%; 3·5 c.c.) with shaking. The mixture was immediately cooled to −50° and then allowed to attain 0° during 4 hours. The ether was removed under reduced pressure at room temperature; the solid (190 mg.; m. p. 123—127°) separating from the acetic acid solution was collected and crystallised from light petroleum (b. p. 60—80°), from which *tetrabromostigmastenyl acetate* separated as clusters of small plates, m. p. 130—131° (decomp.), $[\alpha]_D$ +237°, +239° (*c*, 0·5, 0·5 in benzene) (Found: C, 48·65; H, 6·4; Br, 40·8. $C_{31}H_{46}O_2Br_4$ requires C, 48·2; H, 6·3; Br, 41·4%).

* Part III, *J.*, 1952, 3410.

22 : 23-*Dibromostigmasta*-7 : 9(11)-*dien*-3β-*yl Acetate*.—A solution of tetrabromostigmastenyl acetate (130 mg.) in benzene (10 c.c.) was mixed with one of sodium iodide (0·6 g.) in ethanol (10 c.c.). After 18 hours the mixture was diluted with water, the benzene layer separated, and the aqueous layer extracted with benzene. The combined benzene solutions were washed successively with sodium thiosulphate solution and water. The solution was concentrated to 50 c.c. under reduced pressure and then percolated through a column of alumina (2 × 1 cm.). The filtrate was evaporated and the solid crystallised from methanol–chloroform, giving 22 : 23-*dibromostigmasta*-7 : 9(11)-*dien*-3β-*yl acetate* as needles (70 mg.), m. p. 203—205° (decomp.), $[\alpha]_D$ +35°, +35·5° (*c*, 0·6, 0·7) (Found: C, 60·8; H, 8·2. $C_{31}H_{48}O_2Br_2$ requires C, 60·8; H, 7·9%). Light absorption: Maxima at 2350 (ε = 16,000) and 2420 Å (ε = 18,000) with an inflection at 2500 Å (ε = 12,000). The dibromide gives an orange-red colour with tetranitromethane in chloroform.

Stigmasta-7 : 9(11) : 22-*trien*-3β-*yl Acetate*.—(*a*) A solution of 22 : 23-dibromostigmasta-7 : 9(11)-dien-3β-yl acetate (53 mg.) in a mixture of ether (10 c.c.) and ethanol (15 c.c.) was heated under reflux for 3 hours with zinc dust (300 mg.). The product, isolated in the usual manner, was crystallised from methanol–chloroform, giving *stigmasta*-7 : 9(11) : 22-*trien*-3β-*yl acetate* as plates (28 mg.), m. p. 164—167°, $[\alpha]_D$ +45° (*c*, 0·7) (Found: C, 82·4; H, 10·8. $C_{31}H_{48}O_2$ requires C, 82·2; H, 10·7%). Light absorption: Maxima at 2360 (ε = 17,000) and 2420 Å (ε = 19,000) with an inflection at 2500 Å (ε = 12,500). The compound gives an orange-red colour with tetranitromethane in chloroform.

(*b*) A solution of α-spinasteryl acetate (1·5 g.) in dry chloroform (25 c.c.) was mixed with one of mercuric acetate (3·5 g.) in glacial acetic acid (50 c.c.); mercurous acetate quickly separated. The mixture was shaken for 22 hours, and the mercurous acetate (2·5 g.) was collected and washed with chloroform. The combined filtrate and washings were concentrated under reduced pressure below 50° and the solid (450 mg.), separating on cooling, recrystallised from methanol–chloroform, giving stigmasta-7 : 9(11) : 22-trien-3β-yl acetate as plates (390 mg.), m. p. 159—163° undepressed on mixing with a specimen prepared as described in (*a*), $[\alpha]_D$ +40° (*c*, 2·4) (Found: C, 82·1; H, 11·0%). Light absorption: Maxima at 2360 (ε = 16,000) and 2420 Å (ε = 18,000) with an inflection at 2500 Å (ε = 12,000).

(*c*) A solution of α-spinasteryl acetate (400 mg.) in dry ether (30 c.c.) at 0° was treated with a solution of dry bromine in glacial acetic acid (8%; 2·5 c.c.) with shaking. The solution was cooled to approximately −40°, kept at this temperature for 3 hours, and treated with activated zinc dust (3 g.) and the mixture stirred for 3 hours at −40° and then kept at 0° overnight. After filtration the solution was washed with water and dried (Na_2SO_4), and the solvent removed under reduced pressure. A solution of the solid residue in benzene (100 c.c.) was filtered through a column of alumina (5 × 1·7 cm.), and the column washed with benzene (250 c.c.). The combined benzene filtrates were evaporated and the residue crystallised from methanol–chloroform, giving stigmasta-7 : 9(11) : 22-trien-3β-yl acetate as plates (185 mg.), m. p. 163—166°, $[\alpha]_D$ +46°, +44° (*c*, 0·7, 1·3) (Found: C, 82·2; H, 10·8%). Light absorption: Maxima at 2360 (ε = 16,000) and 2420 Å (ε = 17,000) with an inflection at 2500 Å (ε = 10,500).

Stigmasta-7 : 9(11) : 22-*trien*-3β-*ol*.—A solution of stigmasta-7 : 9(11) : 22-trien-3β-yl acetate (100 mg.) in methanolic potassium hydroxide solution (30 c.c.; 1%) was heated under reflux for 1½ hours. The product, isolated by means of ether, was crystallised from methanol–chloroform, giving *stigmasta*-7 : 9(11) : 22-*trien*-3β-*ol* as needles, m. p. 164—165°, $[\alpha]_D$ +44° (*c*, 0·5) (Found: C, 84·3; H, 11·4. $C_{29}H_{46}O$ requires C, 84·8; H, 11·3%). Light absorption: Maxima at 2360 (ε = 13,500) and 2430 Å (ε = 15,500) with an inflection at 2500 Å (ε = 10,000).

Stigmasta-7 : 9(11) : 22-trien-3β-ol was acetylated in the usual way to give stigmasta-7 : 9(11) : 22-trien-3β-yl acetate which formed plates, $[\alpha]_D$ +45° (*c*, 0·8), m. p. 161—163°.

THE ROYAL TECHNICAL COLLEGE, GLASGOW. [*Received, June 12th*, 1952.]

700. 4-*Methyl* β-*Methylglucoside and Some Further Derivatives of* β-*Methylglucoside.*

By D. I. McGilvray.

A compound designated 4(?)-methyl β-methylglucoside has been described as a liquid (Helferich and Lang, *J. pr. Chem.*, 1932, **132**, 332) but, as the authors indicated, the method of its preparation is open to some doubt. It has now been isolated crystalline following an unequivocal synthesis, which is a development of that previously reported for the preparation of 4 : 6-dimethyl β-methylglucoside (Dennison and McGilvray, *J.*, 1951, 1616).

Experimental.—**2 : 3-***Dibenzyl* **6-***trityl* β-*methylglucoside.* 2 : 3-Dibenzyl β-methylglucoside (Dennison and McGilvray, *loc. cit.*) (11·0 g.) and triphenylmethyl chloride (8·0 g.) in dry pyridine (200 ml.) were heated at 100—105° for 5½ hours. After the solution had cooled, toluene was added until no further precipitation occurred, and the filtrate was poured, with stirring, into aqueous sodium hydrogen carbonate (4 l.; 0·25%). The layers were separated and washed, the aqueous layer once with toluene, and the combined toluene solutions twice with more sodium hydrogen carbonate solution. After drying (Na_2SO_4) of the solution and evaporation of the solvent, the *trityl* derivative remained as a viscous syrup (19·0 g.), $[\alpha]_D^{20}$ −12·6° (in chloroform) (Found: C, 77·5; H, 6·45; OMe, 4·9. $C_{40}H_{40}O_6$ requires C, 77·9; H, 6·5; OMe, 5·0%).

2 : 3-*Dibenzyl* **4-***methyl* **6-***trityl* β-*methylglucoside.* The foregoing compound (7·2 g.) was twice methylated with Purdie's reagents. The syrupy *glucoside* (7·86 g.) had $[\alpha]_D^{20}$ +20·4° (in chloroform) (Found: C, 77·8; H, 6·6; OMe, 9·7. $C_{41}H_{42}O_6$ requires C, 78·1; H, 6·7; OMe, 9·8%).

2 : 3-*Dibenzyl* **4-***methyl* β-*methylglucoside.* The trityl derivative (15 g.) was treated with acetic acid (300 ml.; 80%) for 1 hour at 95—100°. On cooling a crystalline precipitate of triphenylmethanol separated and was removed by filtration, the filtrate dropping directly into ice-water (4 l.). The *glucoside* was recrystallised from light petroleum (b. p. 60—80°), forming fine white needles (5·35 g.), m. p. 87·5—88·5°, $[\alpha]_D^{20}$ +42·9° (in chloroform) (Found: C, 67·6; H, 7·2; OMe, 16·1. $C_{22}H_{28}O_6$ requires C, 68·0; H, 7·2; OMe, 15·95%).

4-*Methyl* β-*methylglucoside.* The benzyl groups were removed from the benzyl derivative (1·7 g.) with sodium ethoxide [from sodium (3 g.)] in ethanol (50 ml.; 97%) (cf. Bell and Lorber, *J.*, 1940, 453). After being heated and then diluted with an equal volume of water, the solution was passed through a column of Amberlite resin IRC 50. Evaporation of the effluent gave a syrup (1·08 g.; OMe, 31%). The product crystallised from ethyl acetate as white needles, m. p. 98—100°. Recrystallisation from *cyclo*hexane–ethanol (4 : 1) gave needles (600 mg.), m. p. 102—103° (not raised by further recrystallisation), $[\alpha]_D^{20}$ −17·6° (in water) (Found: C, 45·8; H, 7·7; OMe, 29·7. Calc. for $C_8H_{16}O_6$: C, 46·1; H, 7·7; OMe, 29·8%).

British Rayon Research Association,
Urmston, Nr. Manchester.

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701. *The Bromination Product of Acridone.*

By S. Kruger.

The bromination of acridone in glacial acetic acid readily yields a dibromo-derivative, which was considered to be 2 : 3-dibromoacridone (Tananescu and Ramontianu, *Bull. Soc. chim.*, 1939, **6**, 486; Heilbron, "Dictionary of Organic Compounds," 1946, Eyre and Spottiswoode, London; Albert, "The Acridines," 1951, Edward Arnold and Co., London). Since Lehmstedt (*Ber.*, 1931, **64**, 2386) has clearly shown that the nitration of acridone leads principally to the 3 : 7-dinitro-compound, it was felt that bromination would be more likely to give an analogous compound rather than the product suggested by Tananescu and Ramontianu.

As these acridones melt above 360°, the 5-*p*-diethylaminophenyl-derivatives, which have lower melting points and are more amenable to purification, were prepared for purposes

of comparison. Thus 3 : 7-dibromoacridone, prepared from authentic 3 : 7-diaminoacridone (Goldberg and Kelly, *J.*, **1946**, 102) by means of a double Sandmeyer reaction, was converted into 3 : 7-dibromo-5-*p*-diethylaminophenylacridine, which gave no depression of melting point when mixed with the corresponding derivative of Tananescu and Ramontianu's dibromo-compound.

Authentic 3-bromoacridone similarly gave a dibromo-derivative, identical with synthetic 3 : 7-dibromoacridone.

Experimental.—Bromination of acridone. Acridone (5 g.) was dissolved in glacial acetic acid (500 ml.), and bromine (5·2 g.) in glacial acetic acid (50 ml.) added with shaking at room temperature. The bright yellow precipitate, which formed almost immediately, was filtered off, washed, dried, and recrystallised from nitrobenzene. The yield was almost quantitative. The yellow needles, m. p. >360°, gave a violet-blue fluorescence in alcohol, which became greenish-yellow on the addition of a few drops of alkali (Found : C, 44·3; H, 2·1. Calc. for $C_{13}H_7ONBr_2$: C, 44·2; H, 2·1%).

Bromination of 3-bromoacridone. Bromine (2·4 g.) in glacial acetic acid (20 ml.) was added with shaking to 3-bromoacridone (4 g.) (Ullmann and Tedesco, *Annalen*, 1907, **355**, 341) in glacial acetic acid (600 ml.) The bright yellow precipitate was filtered off, washed, dried, and recrystallised from boiling nitrobenzene; it formed yellow needles, m. p. >360°.

3 : 7-*Dibromoacridone.* 3 : 7-Diaminoacridone (Goldberg and Kelly, *J.*, **1946**, 102) (10 g.) was dissolved in excess of aqueous hydrobromic acid and diazotised with a slight excess of sodium nitrite at 5—10°. Excess of nitrite was destroyed by the addition of a small quantity of urea. During the diazotisation a pale yellow precipitate (probably the diazonium salt) was formed, which was dissolved by slightly raising the temperature. The solution was then filtered and a solution of cuprous bromide (13 g.) in hydrobromic acid (100 ml.) was added slowly with stirring; nitrogen was evolved and a brown precipitate was formed. The reaction was completed by warming the mixture on a water-bath till the evolution of nitrogen had ceased (about 4 hours). The solid was filtered off, dried, and recrystallised from boiling nitrobenzene; 3 : 7-dibromoacridone formed small greyish-yellow needles (6 g., 39%), m. p. >360° (Found : Br, 44·9. Calc. for $C_{13}H_7ONBr_2$: Br, 45·3%).

3 : 7-*Dibromo*-5-p-*diethylaminophenylacridine.*—Each of the above-mentioned dibromoacridones was treated as follows : Dibromoacridone (1 g.), freshly distilled diethylaniline (2 g.), and phosphorus oxychloride (1 g.) were heated in a water-bath for 2 hours. The mixture was then poured into excess of sodium hydroxide solution, and the diethylaniline removed by steam-distillation. The remaining solid was filtered off, dried, and recrystallised, first from benzene and then from toluene; it formed orange prisms, m. p. 278—279°, in each case. None of these samples of *dibromodiethylaminophenylacridine* gave a depression of melting point when mixed with either of the others (Found : C, 57·3; H, 4·4; N, 6·1. $C_{23}H_{20}N_2Br_2$ requires C, 57·0; H, 4·1; N, 5·8%).

I am indebted to Burroughs Wellcome and Co. (Australia) Ltd. for a grant with which this work was carried out, and also to Professor R. H. Thorp for his encouragement and interest.

Department of Pharmacology, University of Sydney. [*Received, May 27th*, 1952.]

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702. *The "Cross and Bevan" Cellulose of* Posidonia australis.

By D. J. Bell.

Posidonia australis, a monocotyledon of terrestrial character, inhabits sheltered shallow seas off South Australia. Fibrous remains of the plant accumulate in quantity on the beaches where only slow natural decomposition takes place. Earl (*J.*, 1924, **125**, 123) and Arneman and Earl (*J. Roy. Soc. N.S.W.*, 1929, **63**, 44) prepared acetates {$[\alpha]_D$ *ca.* −40° (in chloroform)} (Barnett, *J. Soc. Chem. Ind.*, 1921, **40**, 8T) from "Cross and Bevan" celluloses derived from both leaves and residual fibres, and obtained from them mixed α- and β-methyl-D-glucosides, in 77·5% yield (cf. Irvine and Hirst, *J.*, 1922, **121**, 1588). They suggested that the chief polyglucose of *Posidonia* fibre differed in some way from the usual form of cellulose which yields an acetate with $[\alpha]_D$ *ca.* 22°. Subsequently,

celluloses from wood (Barsha and Hibbert, *J. Amer. Chem. Soc.*, 1936, **58**, 1006; Bell, *Biochem. J.*, 1938, **32**, 699), pear cell-wall (Hirst, Isherwood, Jermyn, and Jones, *J.*, 1949, S182), and marine algae (Percival and Ross, *J.*, 1949, 3041) have been shown to be based on the same fundamental chemical plan as cotton. It therefore appeared of interest to re-examine the *Posidonia* polysaccharide. Through the kind co-operation of Dr. H. B. S. Womersley of the University of Adelaide Botanical Department, generous supplies of both the freshly gathered leaves and the residual fibres were made available.

" Cross and Bevan " celluloses were prepared from both sources, as described by Dorée (" The Methods of Cellulose Chemistry," London, 1947, p. 352); the materials contained appreciable amounts of pentosan. Acetylation (Barnett, *loc. cit.*) gave triacetyl derivatives (pentosan-free) having, in chloroform, $[\alpha]_D$ $-22°$ ($\pm 2°$) from the residual fibre, and $-24°$ ($\pm 2°$) from the leaves. Six treatments, at room temperature, of the acetate (5·0 g.) suspended in dioxan with large excesses of methyl sulphate and 30% (w/v) sodium hydroxide solution gave a trimethyl hexosan (2·2 g.) (Found, OMe, 44·7%), $[\alpha]_D$ $-6°$ (in chloroform); the average loss per methylation treatment was therefore 4·65%. Hirst *et al.* (*loc. cit.*) found $[\alpha]_D$ $-7°$ for pear trimethyl cellulose, and Bell (*loc. cit.*) found wood trimethyl cellulose to be inactive. Haworth, Hirst, Peat, and Averill (*J.*, 1939, 1885) found values between $-3°$ and $-8°$ for specimens of cotton trimethyl cellulose, prepared under different conditions.

Hydrolysis (Bell, *Biochem. J.*, 1935, **29**, 2031) of trimethyl cellulose from *Posidonia* gave 94% recovery of an almost entirely crystalline trimethyl hexose which was freed from traces of lower homologues by chromatography (Bell, *J.*, 1944, 473). Paper chromatography indicated the presence of 2 : 3 : 6-trimethyl glucose uncontaminated by any isomers. Dissolved in dry methanol, containing 2% (w/v) of dry hydrogen chloride, the substance showed $[\alpha]_D$ $+60°$ (2 minutes) falling to $-35°$ (constant) in 450 minutes (cf. Irvine and Hirst, *J.*, 1922, **121**, 1213), thus confirming the 2 : 3 : 6-structure.

The acetates prepared by Earl may have retained some xylan derivatives. Although no reference can be found to the magnitude of the $[\alpha]_D$ of xylan acetates, xylan itself and its methylated derivative have large negative rotations. It is therefore concluded that *Posidonia* cellulose, when exhaustively " delignified," is not significantly different from celluloses of other plants.

The resistance to natural decomposition may be associated with the manner in which the fibres are impregnated by " lignin." The leaves and the residual fibre were not attacked by either snail-gut enzymes or the rumen flora of the sheep. The " Cross and Bevan " celluloses from each source were rapidly attacked by both digestive systems.

The author is grateful to Dr. I. A. McDonald for carrying out ruminant digestion tests and to Dr. D. H. Northcote for providing snail-gut preparations.

THE BIOCHEMICAL LABORATORY, CAMBRIDGE. [*Received, June 17th*, 1952.]

The Chemical Exploration of the Stratosphere.

HUGO MÜLLER LECTURE, DELIVERED BEFORE THE CHEMICAL SOCIETY AT BURLINGTON HOUSE ON MARCH 27TH, 1952, AND AT THE UNIVERSITY, MANCHESTER, ON APRIL 23RD, 1952.

By F. A. PANETH.

THE discovery of the stratosphere, and all research concerning it, belongs to this century; but the chief chemical problem involved goes right back to the period when our science was born, and it seems to me that even to-day we can learn something from the procedures, successes, and mistakes of the early chemists who probed into the nature of the atmosphere.

Modern chemistry arose in the middle of the eighteenth century from the scientific study of the historical four elements. It became clear that " earth " was too vague a term for analytical chemistry and that many different earthy substances had to be distinguished. The explanation of " fire," and of the accompanying phenomena of light and heat, was recognized as belonging to the realm of physics. A clear chemical answer could soon be given for " water "; James Watt was the first who stated that it could be synthesized by combining two gases, and thanks to the further researches of Cavendish and Lavoisier the question of its nature was soon definitely settled.

It proved to be much more difficult to come to a decision about " air ". The work of Scheele, Priestley, and Lavoisier had shown that the atmosphere, like water, consisted of two gases; but was it also a chemical compound, or only a physical mixture? Some chemists, for instance, Dalton's friend Thomas Thomson,[1] strongly advocated for air the formula N_4O, and Dalton himself abstained as late as 1838 from a clear-cut decision between the two possibilities.[2] The majority of their contemporaries, however, considered atmospheric air to be a mixture of nitrogen and oxygen whose composition was dependent on meteorological conditions. It is well to remember that the "eudiometer", in accordance with its etymology, was originally an instrument for measuring the " goodness ", *i.e.*, the oxygen content, of air.

To-day we know that the adherents of the view that air is a mixture, were right; but in their strongest argument, the variability of its composition, they were entirely mistaken. They over-estimated the accuracy of their methods and believed that changes in the results which were due to experimental errors indicated actual fluctuations in composition. We shall see that the same mistake was made much later in the analyses of stratosphere air.

If we remember on what methods the old chemists had to rely for the analysis of air, we are not astonished at the spurious figures found by many but are filled with admiration for the few who handled these methods so skilfully that correct results were obtained. At the beginning the nitric oxide eudiometer was used; the diminution of the volume of an air sample, when mixed with a certain volume of nitric oxide and kept over water, was taken to be a measure of the oxygen present. But the nitric oxide employed was far from pure, and each chemist chose his own factor for calculating the oxygen content from the decrease of gas volume. No wonder that the results varied widely, especially if the analysis had to be carried out under unusual conditions. As gifted a scientist as the young Alexander von Humboldt during a sea voyage reached the conclusion that the oxygen content of air rose to more than 30% on fine moonlit nights. Others observed that South Kensington air was much richer in oxygen than that of London, and that the weather had a marked influence. Cavendish, on the other hand, as early as 1781, with his uncanny experimental skill came to the conviction that no variations in the oxygen content of air occurred, although he too had no better instrument than the nitric oxide eudiometer which, according to a contemporary critic, was suffering from no less than 20 different sources of error.

It was a great step forward when Volta introduced the hydrogen eudiometer, especially after Gay-Lussac and Humboldt, by experimenting with it, had stated that exactly two volumes of hydrogen disappeared with one volume of oxygen when the two gases were exploded. Omitting a few other methods, *e.g.*, those based on the oxidation of phosphorus or iron sulphide, or the absorption of oxygen by pyrogallol, we want to single out the copper eudiometer, introduced by von Jolly in 1850,[3] because we found this method most convenient in our own experiments. If metallic copper is heated to the right temperature, one can be certain that all the oxygen gas present in an air sample disappears.

Determining the oxygen content of air was a subject which for decades not only was a hobby

with many amateurs of chemistry and meteorology, but occupied the interest of almost every great chemist; we find, beside the famous names already mentioned, those of Berthollet, Regnault, Bunsen, and many others. In a review of the literature one fact becomes obvious: the better the method, and the greater the personal experience of each investigator, the smaller were the differences found. Outstanding in many respects was the world-wide survey carried out by Regnault [4] in the middle of the nineteenth century. He enlisted the help of scientists in many countries who provided him with air samples; even though some of these showed slight variations—which Regnault took to be significant, although they were certainly due to faulty sampling or storage—he came to the conclusion that the percentage of oxygen in air is almost invariably 20·9. Amongst the later investigators two are specially to be mentioned in our brief survey: U. Kreusler,[5] who in 1885 in Bonn by a very long and painstaking series of experiments proved that meteorological conditions are without influence; and F. G. Benedict,[6] who in 1912 in Washington confirmed this statement with higher precision and expressed the main result very well in the illuminating sentence: "Air is a physical mixture with the definiteness of composition of a chemical compound."

Benedict's statement is, of course, not applicable to more or less closed areas in which the oxygen content may be reduced by the combustion of fuel and the respiratory exchange of organisms, or increased by the assimilation of carbon dioxide in plants; but, as in these processes almost equal volumes of oxygen and carbon dioxide replace each other, they leave the nitrogen percentage in air practically unaltered. We are, therefore, on still safer ground if we restrict Benedict's statement to this gas and, following A. Krogh,[7] declare that the percentage of nitrogen in the atmosphere is a geophysical constant which can be determined with a high degree of accuracy.

"Atmospheric nitrogen" in older literature always means, of course, nitrogen plus argon, plus the negligibly small amounts of the inert gases helium, neon, krypton, and xenon. We shall see later than these inert gases are most useful standards in stratosphere research, and we are therefore interested in the question of their individual constancy in ordinary atmospheric air. Only for two of them, argon and helium, have direct investigations been carried out. Moissan [8] analysed air samples from several towns and also from over the sea, and found—with one doubtful exception—no variations. The likelihood of geographical influences seemed somewhat greater in the case of helium because of the very large quantities of this gas entering the air in certain areas, as *e.g.*, the petroleum fields of Texas. As we intended in our stratosphere research principally to make use of helium, we thought it necessary to test the uniformity of its distribution over the surface of the earth. Regnault, in his world-survey of oxygen, had insisted that his samples be collected by aspiration of air and sealed in glass; that restricted the number of his helpers to fairly well-instructed persons. We extended their possible number by asking only that a bottle be filled with water, then the water poured out and the bottle well closed with a cork or rubber stopper. It is obvious that one cannot be sure of the oxygen content remaining unaltered in such a bottle, but we thought it anyhow much safer to base our research on the relationship of the inert gases to the nitrogen content. Thanks to the help given by the Meteorological Office of the Air Ministry and to many private persons we obtained samples from all over the world, as can be seen from the points indicated on the map (Fig. 1). Our subsequent analyses showed that the helium content of atmospheric air is as much of a geophysical constant as is the nitrogen content.[9] There is no reason to doubt that what has been found for argon and helium holds also for neon, krypton, and xenon.

There are, however, other constituents of atmospheric air which are certainly not constant. Water vapour is obviously so variable that for our purpose—not for meteorological questions—it is best to neglect it completely by referring always to dried air. Hydrogen is present in air only in such a small amount and is so difficult to exclude as a contamination that very little is known about its quantity,[10] and less still about its constancy. In several instances traces of dinitrogen tetroxide, ammonia, sulphur dioxide, and carbon monoxide have been reported, but it may be that their occurrence is limited to the neighbourhood of human habitations and industrial activities. Recently, by spectroscopic means, methane and nitrous oxide have also been identified in the atmosphere,[11] in quantities not exceeding those of the rarest of the rare gases.

For our present survey we may neglect these constituents; it would, however, be incomplete if we did not pay attention to one gas which is rare near the surface of the earth but proportionately much more abundant in the upper atmosphere: the gas ozone. Schönbein, the discoverer of ozone, was also the first who believed in its presence in the air and in the possibility of measuring its quantity by the simple device of strips of paper soaked in solutions of potassium iodide and

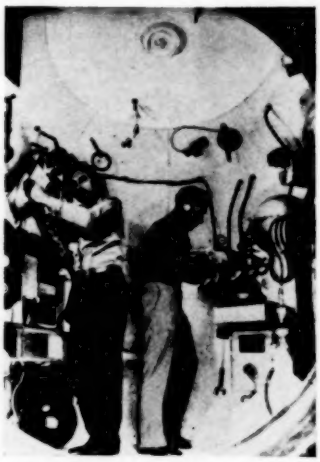
PLATE I.

Gay-Lussac collecting air during a balloon flight in **1804**, *by turning the stopcock of an evacuated glass vessel.* (*The picture is included in J. Howard Appleton's "Beginners Handbook of Chemistry," Chautauqua Press, New York,* **1888**; *no reference to its origin is given.*)

PLATE II.

Spherical gondola for the stratosphere flight of G. A. Prokofiev, K. D. Godunov, and Birnbaum in **1933** (*see also ref.* **30**). [Reproduced, by permission of The New York Times, from G. Heard, "Exploring the Stratosphere," T. Nelson & Sons, Ltd., Edinburgh, **1936**.]

PLATE III.



Captain A. W. Stevens (*left*) *and Captain O. A. Anderson in the Gondola of "Explorer II" in* **1935**. *The evacuated vessel for the stratosphere sample can be seen on the right* (*see also ref.* **32**). [Reproduced from G. Heard, "Exploring the Stratosphere," T. Nelson & Sons, Ltd., Edinburgh, **1936**.]

PLATE IV.

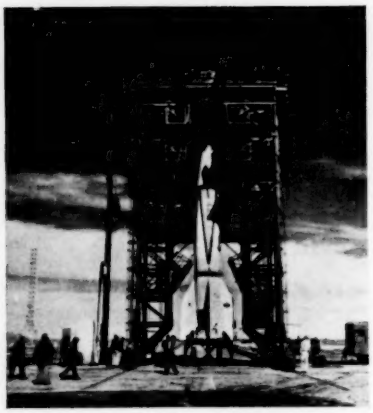
Mr. L. H. G. Dines launching a sounding balloon, with attached mechanism for air sampling, at Kew Observatory in **1936** (*see ref.* **26**).

(*To face p.* 3652

PLATE V.

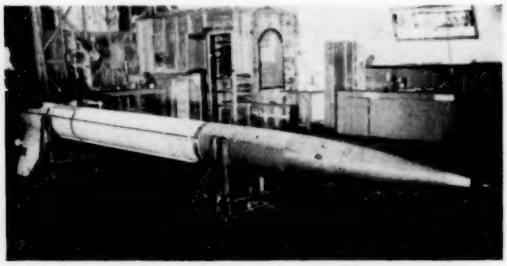
German V-2 rocket, converted in U.S.A. for scientific purposes.

PLATE VI.



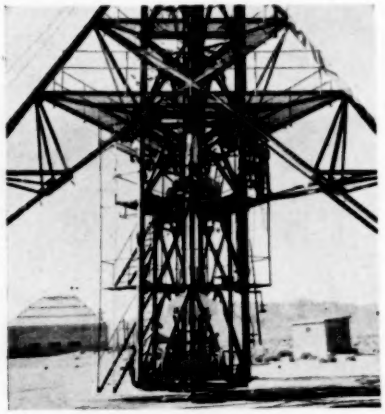
German V-2 rocket standing on its fins inside a gantry for the final instrumentation and fueling. Before the flight the gantry is rolled away.

PLATE VII.



Aerobee rocket built in the Applied Physics Laboratory of Johns Hopkins University. Propulsion is accomplished in two stages. A solid propellant "booster" rocket brings the velocity to about 1000 *ft. per second, then it falls away, and the sustaining liquid-fuel motor takes over, accelerating the rocket to about* 4000 *ft. per second (see ref.* 27).

PLATE VIII.



Aerobee rocket standing inside the tower through which it is to be fired.

PLATE IX.

Aerobee rocket at the moment of being shot out of the tower.

PLATE X.

Front part of Aerobee rocket, with nose cone which is thrown off during the flight just before the sampling bottles are opened. The arrangement of the three bottles can be seen below the cone.

PLATE XI.

Arrangement for opening and closing of the copper tube which leads into the evacuated steel bottle. Both mechanisms are operated by the explosion of black powder; opening is achieved by a piston which breaks off the end of the copper tube, and closing by compression of two steel jaws which effect cold welding of the copper tube at a point nearer to the bottle (see also Plate XIII.)

PLATE XII.

***Part of an Aerobee rocket, with the three** bottles containing **stratosphere air,** after being landed by parachute.*

PLATE IX.

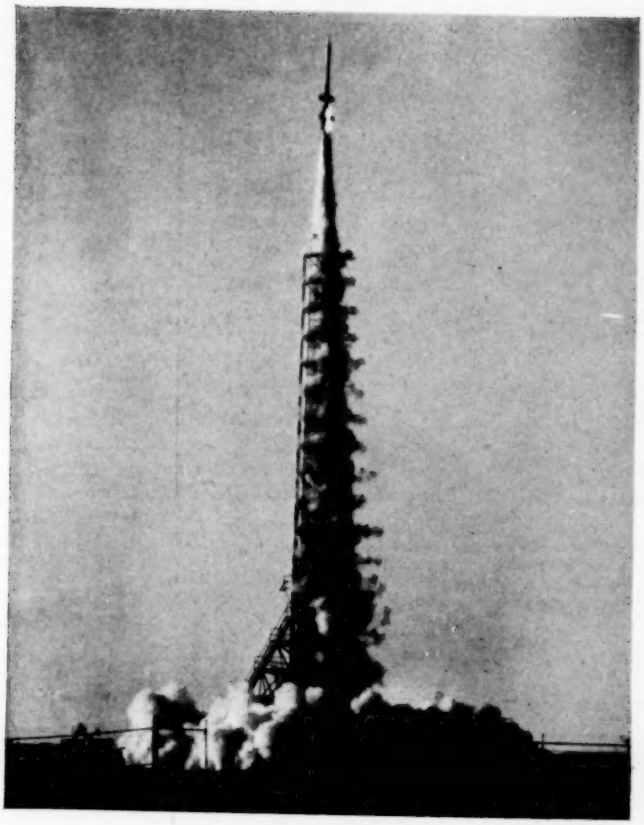


PLATE X.

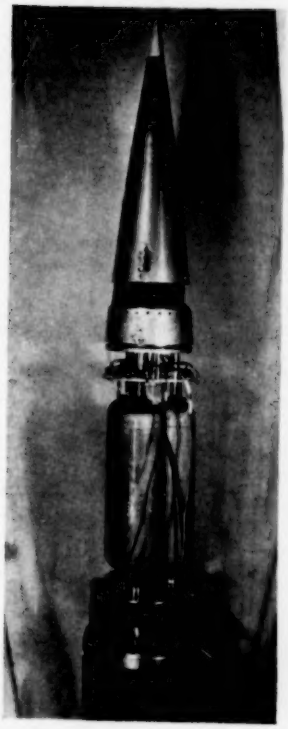


PLATE XI.

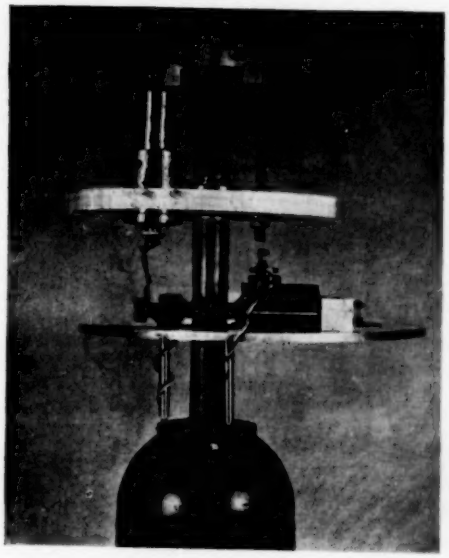


PLATE XII.

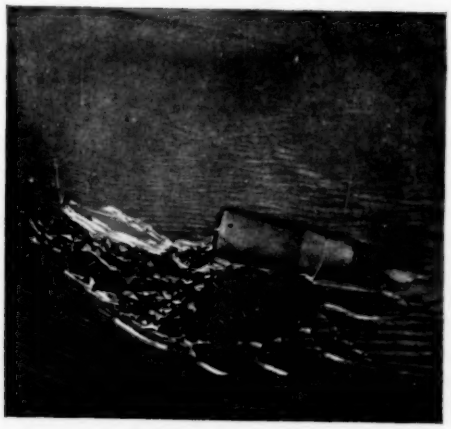
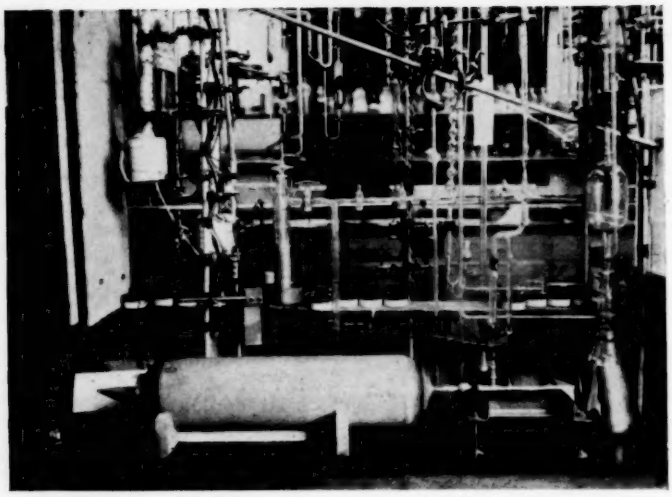
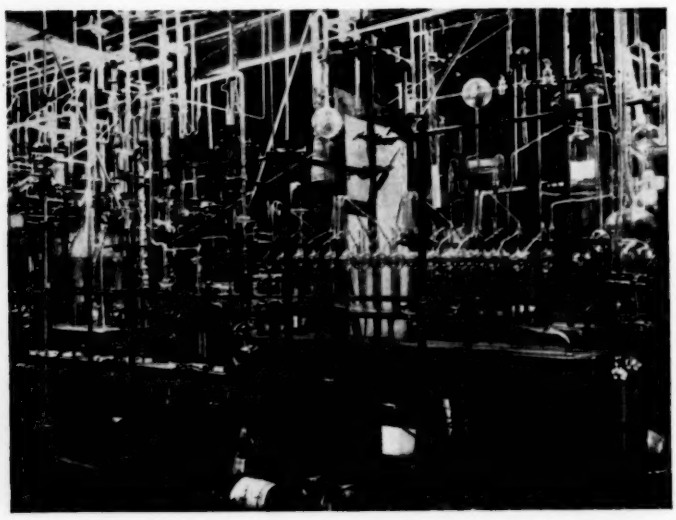


PLATE XIII.



Steel bottle containing stratosphere air connected with the gas-analysis apparatus. On the left can be seen the flat edge of the copper tube which was cold-welded during the flight of the rocket; on the right the metal bellows which allow a needle to be pressed against a copper membrane inside the steel bottle, thus making a hole through which the gases can be pumped into the apparatus for analysis.

PLATE XIV.



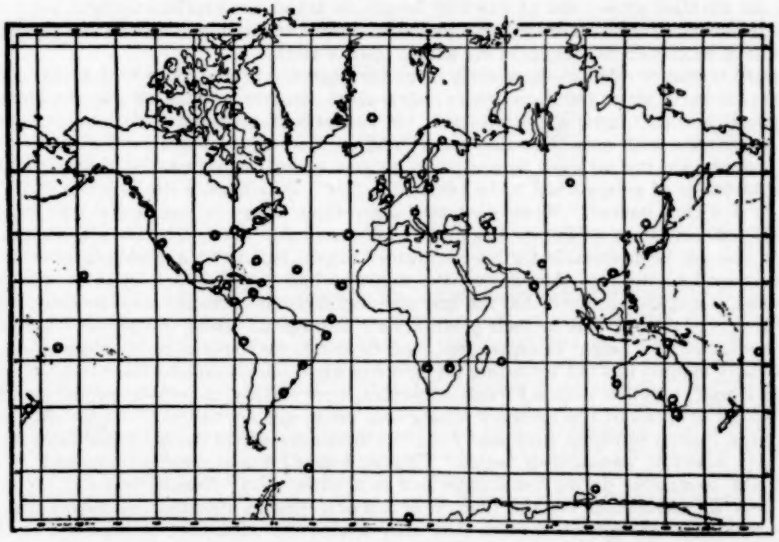
Part of the Durham apparatus for the micro-analysis of rare gases. In the foreground can be seen the fractionation column for the separation of helium and neon.

[Photographs from which Plates X and XI were made were taken by the photographer of the Engineering Research Institute of the University of Michigan; the other photographs of the V-2 and Aerobee Rockets are by U.S. Signal Corps photographers.]

starch. Similarly, as half a century earlier the salubrity of air was supposed to vary with its oxygen content, so now medical men ascribed it to the presence of ozone, and the apparent simplicity of its estimation from the intensity of the blue colouration of the paper strips inaugurated a period of " ozonometry " in which an even greater number of qualified and unqualified people participated. It has been calculated that literally millions of such ozone measurements have been made.[12] Although little of permanent value was achieved, it seems that some seasonal variations were correctly established, and as an influence of the ozone content of air on the human well-being [13] is not *a priori* impossible, we must admit that ozonometry was not quite such a wild-goose chase as the old eudiometry.

There came, however, a reaction when it was realized that Schönbein's potassium iodide test, not being specific for ozone, may indicate other oxidising agents in air, especially dinitrogen tetroxide, and for a while only the well-known spectroscopic proof for atmospheric ozone was considered to be reliable. In 1938, J. L. Edgar succeeded in my laboratory in London in concentrating atmospheric ozone by condensing it on silica gel, and then in measuring the

FIG. 1. *Places from which air samples have been analysed for their helium content* (*see ref.* 9, *p.* 94). [Reproduced, by permission, from *Proc. Roy. Soc.*, 1945, *A*, **185**, 94.]



same sample in two ways—spectroscopically and by the iodide test. The agreement was very satisfactory, and he could also show that the danger of a confusion with dinitrogen tetroxide was small and could easily be avoided.[14] These experiments paved the way to a trustworthy chemical measurement of atmospheric ozone. Between the years 1939 and 1941 in my Durham Laboratory E. Gluckauf, H. G. Heal, and G. R. Martin [15] developed a self-recording chemical ozonometer. The basic idea was to liberate iodine by the ozone in a potassium iodide solution and to use its depolarizing effect on a platinum electrode for the production of a minute electric current which, after amplification, triggered an automatic burette; the apparatus measured the ozone content of air every few minutes and worked without supervision for 24 hours. These experiments had to be discontinued during the war, but it is gratifying to know that recently Bowen and V. H. Regener [16] at the University of New Mexico have taken up our method and hope to use it, with slight alterations, for the automatic recording of ozone in the upper atmosphere. No results have so far been reported, but it is very likely that in the near future the measurement of ozone by this or another chemical method will have to be included in a report on the chemical exploration of the stratosphere.

If, returning now to the constant constituents of atmospheric air, we take it for established that their relative proportions do not change from place to place, or from day to day, have we to assume then that the total atmosphere has the same percentage composition? To be sure,

very few scientists expected that after Dalton's law of partial pressures had been formulated in 1826. Since the days of Descartes, Pascal, and Boyle it had been known that the density of air diminished with height according to the barometric formula and, if each gas behaved as if it alone were present, then the rate of this diminution had to be slower for the light than for the heavy gases; in other words, a sample of air taken from a certain height should be relatively enriched in the lighter constituents.

It is of some historical interest that even before Dalton's time this conclusion had been reached. In 1800 Berthollet, who was very sceptical about reports that variations of the oxygen–nitrogen ratio had been found in not very distant villages, added: "However, one has to make an exception for places high above sea level. The difference in the specific weight between oxygen and nitrogen gas, which have only a very feeble action on each other, explains the difference which has been found in their proportions." [17] It is only fair to see, with Kreusler, in this passage a statement coming very close to an enunciation of Dalton's law; and similar considerations had apparently as early as 1798 prompted Humboldt to analyse air collected during a balloon flight at an altitude of 1300 metres, and de Saussure to do the same with air from several mountain tops. As a curiosity it may also be mentioned that about the same time a professor claimed that he had succeeded in separating the oxygen and nitrogen by simply allowing an air-filled glass tube of five feet length to stand undisturbed upright for a year; but this remarkable experiment which Chladni mentions in his famous book on acoustics,[18] seems to have succeeded only once, in my native town Vienna.

For some reason or other in those early days one expected to find more spectacular changes in the composition of air on rising anywhere only a short distance into the air than by attaining, on the ground, great altitudes above sea level. It was, of course, known that on high mountains people can breathe with only little discomfort and without any damage to their health; but the first ascent into the air even in a captive balloon seemed so dangerous that experiments with various kinds of animals had to be performed first. So a cock, a duck, and a sheep were sent up in a wicker basket. When examined after their return it was found that the cock was clearly suffering from an indisposition; but the conclusion reached by the experts that the higher air had not been suitable for his respiratory organs had to be abandoned when his ailment was traced to the fact that during the flight he had been trodden upon by the sheep. Nevertheless, it was thought best that the first men to follow the animals should be two criminals under sentence of death; but in their place a very courageous young technician volunteered, spent five minutes at a height of eighty feet, and described his experience as exhilarating.[19]

These early ascents in 1783, including the first free flight undertaken by the same technician, Pilâtre de Rozier, together with a French nobleman, were mainly meant as public spectacles, and the hot-air balloons of the brothers Montgolfier never got beyond that stage. But simultaneously the French physicist Professor J. A. C. Charles developed the hydrogen-filled balloon and with it scientific aeronautics began. Charles himself made observations with a thermometer and barometer during the flights, and in a letter to Sir Joseph Banks at the end of 1783, a year so memorable for the history of science, Joseph Priestley expressed the hope that the balloons "though at present they only amuse the idle, may in time answer some important purposes in philosophy, enabling us to explore the upper regions of the atmosphere." [20]

It is probably right to say that, in the minds of most scientists, foremost amongst these purposes was the wish to prove the correctness of the law of partial pressures by analysing air from the upper regions and to show that its oxygen percentage had decreased. This seemed to be almost a foregone conclusion, as this observation had been more than once reported on mountain air. But when in 1804 one of the very best chemists, Gay-Lussac, examined air which he himself had sampled in a balloon flight at a height of more than 6½ km. (see Plate I) he found no difference.[21]

Gay-Lussac was to my knowledge the only scientist who applied himself to both the difficult tasks of collection of an air sample from as great a height as possible and its analysis with as great an accuracy as possible. Usually the analysis was entrusted to a chemist who had nothing else to do but to perform this job correctly; in most cases he probably did so and if, nevertheless, for decades the results were inconsistent and contradictory, the reason must be sought in the dangers inherent in the collecting and storage of air. Illuminating examples of this can be found in Dalton's protocols.[22] Dalton always observed that air collected by himself on the tops of mountains, or sent to him by a friend from heights in Switzerland, contained a lower percentage of oxygen than Manchester air; but it did not occur to him that the longer time during which mountain air had been stored in wet bottles in contact with cork might have something to do with the observed effect. In at least one case he even noted that after two more weeks the

oxygen content had further decreased; this seemed to him incomprehensible in view of the fact that the bottles had been kept carefully corked. We shall see later that even to-day the difficulty in determining the oxygen content of stratosphere air does not lie with the analysis, but with the sampling.

Although Dalton thought that qualitatively he had confirmed the expected diminution of oxygen content, he realised that the effect was far less than the theory of the independent behaviour of oxygen and nitrogen predicted, and he correctly ascribed this to the disturbing influence of winds.[33] He recognized for the first time how important the chemical investigation of the composition of the atmosphere may be for the meteorological problem of the efficiency of winds. It is this importance, much more than the purely chemical interest, which inspired the many difficult, and also very expensive, researches on the constituents of the atmosphere at ever greater heights.

Gay-Lussac's balloon ascent was followed by a few others from which air samples were brought back. In more recent times the analysis of these samples was undertaken in the expectation, not of finding a decrease in the oxygen content—which was known by then to be at the best very small—but a much more marked increase in the light gases hydrogen, helium, and neon (see Table 1). But if the carrying balloon is filled with hydrogen, no sampling

TABLE 1. *The constant constituents of the atmosphere.*

	Mol. wt. (O = 16·000)	Density (Air = 1·000)	Percentage in air
Hydrogen	2·016	0·0695	5×10^{-5}
Helium	4·003	0·138	$5{\cdot}2 \times 10^{-4}$
Neon	20·183	0·695	$1{\cdot}8 \times 10^{-3}$
Nitrogen	28·016	0·967	78·09 }
Oxygen	32·000	1·105	20·95 } 100
Argon	39·944	1·379	0·93 }
Carbon dioxide	44·01	1·529	0·03 }
Krypton	83·7	2·868	1×10^{-4}
Xenon	131·3	4·525	9×10^{-6}

device in the gondola will be safe against contamination from this overwhelming source, and the analytical technique of most of the chemists was not good enough to allow them to determine separately hydrogen, helium, and neon in small quantities of air; so they confined themselves to the statement that at an altitude of no more than eight or nine km. they had found a light " residual " gas which, they thought, indicated the presence of helium and neon. In most cases this ill-defined " residual " gas seems to have consisted of hydrogen from the balloon, and it is rather astonishing that well-known meteorologists in the twenties of this century declared themselves satisfied that the prediction of an increase of the lighter constituents of the atmosphere with height had been proved correct by these superficial analyses.[10] Even the purely meteorological knowledge of the constant mixing of the atmosphere by winds should have made them sceptical about the chemists' findings.

Since the early part of this century it has, however, been known that we have to distinguish at least two different regions of the atmosphere. When thermometers were sent up in sounding balloons, they registered a fairly steady decrease of the temperature up to a height—in our latitude —of about 11 km.; but from there onwards the temperature remained constant, at approximately 219° K (−54° C), up to the greatest height accessible to direct measurements. It was then assumed that no large-scale mixing of the atmosphere could occur in such a region without temperature gradient; this supposedly quiet layer was, therefore, distinguished as the " stratosphere " from the lower " troposphere," the place of all meteorological changes.

To-day we know that the structure of the atmosphere is much more complicated. Indirect evidence, collected mainly from observations on meteors and measurements on the propagation of sound and radio-waves, makes it certain that the region of constant temperature reaches only up to about 25 km.; from that height onwards the temperature rises, but after attaining a maximum of perhaps 280° K at 50 km. it falls again, passes through a minimum of about 190° K at the height of 80 km., and finally rises, uninterrupted, to more than 1000° K.

The explanation of these temperature changes presents a very difficult problem for the meteorologist and theoretical physicist. The help of the chemist is essential because the heating effect of solar radiation depends on the nature of the gases, and it is for this and similar reasons important for them to know the chemical composition of the atmosphere at all heights. We have seen that all reports about an increase of the lighter constituents in the upper part of the

troposphere have been erroneous; but if in the stratosphere, or in certain layers of the stratosphere, stillness should reign, we may hope to find the long-sought effect of gravitational separation, and we may even expect to detect in the highest strata the rare gas helium as the predominent constituent.

Fig. 2, after J. Bartels,[24] shows the height-dependence of the partial pressures of argon, oxygen, nitrogen, and helium, calculated on the assumption that from 12 km. onwards the atmosphere is free from disturbances and its temperature throughout 219° K. Fig. 3 gives, after S. Chapman and E. A. Milne,[25] the percentage composition of air at various heights for the same temperature and the case that disturbances cease at 20 km. It is true that spectroscopic and other observations make an effect of this magnitude unlikely; the light of the aurora, for instance, indicates that at heights of several hundred km. nitrogen and oxygen are still the main gases of the atmosphere. But even a small change in composition, if established by chemical analysis, would be important because it would indicate the absence of air currents—not only for minutes or hours, but, depending on the density and temperature of the atmosphere at the

FIG. 2. *Diminution, with height, of the partial pressures of the atmospheric gases, on the assumption that there is stillness from 12 km. upwards (see ref. 24, p. 135).*

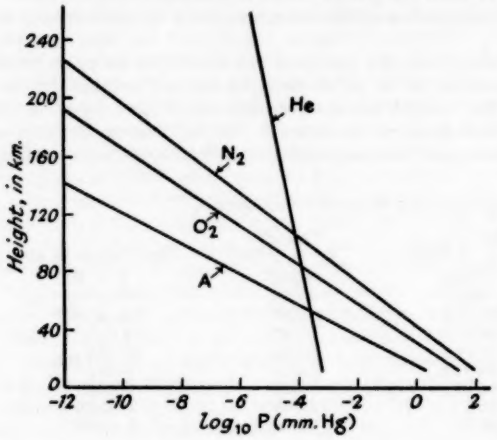


FIG. 3. *Composition of the atmosphere at different heights, on the assumption that there is stillness from 20 km. upwards (see ref. 25, p. 379).*

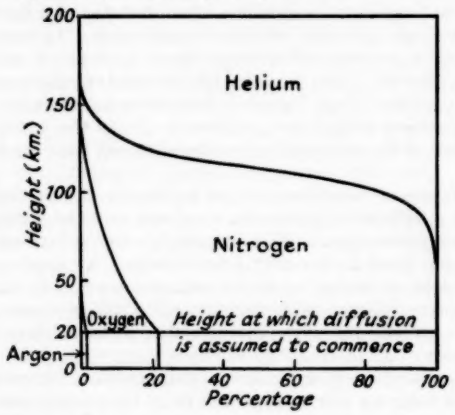
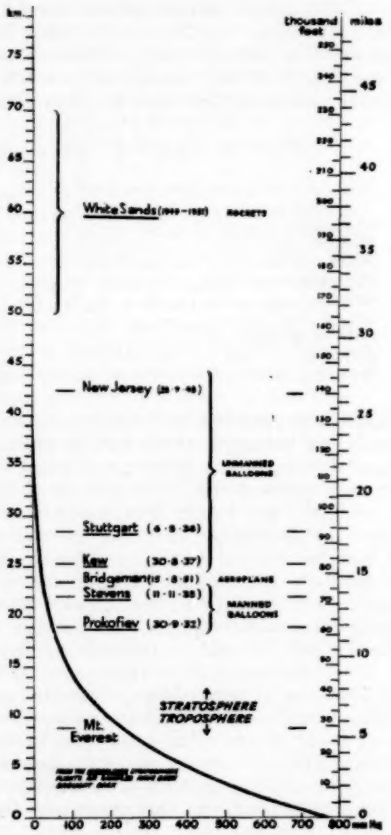


FIG. 4. *Sampling of stratosphere air at different heights. The curve indicates the barometric pressure.*



height in question, for weeks, months, or years. The establishment of an equilibrium in the gravitational field of the earth according to the law of partial pressures is a very slow process: its disturbance by winds is a very fast one. If, therefore, the chemists should find at least an approximation to this equilibrium, we may safely conclude that we have reached a region, or the neighbourhood of a region, of long-lasting stillness. Such a discovery cannot fail to be of consequence to meteorology and atmospheric physics.

All attempts at analysis of stratosphere air have to face two difficulties: the collection of reliable samples, and their exact analysis. Let us first consider the various methods by which the samples can be obtained.

The first men to enter the stratosphere were, in 1931, A. Piccard and his assistant. Their technique of the closed spherical gondola was copied in subsequent stratosphere flights. One of them, undertaken by Russian explorers (see Plate II), brought air back from 18·5 km. This height was surpassed by an American stratosphere balloon flight in 1935, which attained 22 km. and from which also air samples were delivered to a chemical laboratory; one of the evacuated vessels of 22-l. capacity which were used by the pilots for this purpose, is visible on the right side of Plate III, attached to the wall of the gondola.

From Fig. 4 it can be seen that the greatest height reported for aeroplanes is above the last-mentioned record flight of a manned balloon. But aeroplane flights at maximum height are so difficult and demand the attention of the pilot so completely, that he cannot be expected to work any scientific apparatus. The little he might be able to do can quite as well be performed by automatic devices attached to an unmanned balloon, and these sounding balloons can far surpass any altitude within reach of men. Furthermore, these flights can be done at very low cost and may therefore be arranged frequently—a very essential point in all meteorological investigations where the collecting of a statistical material is necessary. Such balloons are either made of rubber, closed, and expand as they go up; or they are fabricated of a plastic material, open at the bottom, and have constant volume. The higher the altitude they are meant to reach, the smaller has to be their payload, but up to 30 km. they can carry apparatus of the order of 100 lb.

These pilot balloons have been very useful in collecting air samples up to about 30 km.; Plate IV shows the launching of a rubber balloon, carrying an evacuated glass vessel of 300-c.c. capacity which was to be opened and closed at the top of the flight by a simple electrical device [26] (see Fig. 5). As will be explained later, the analyses of these samples still failed to solve the main problem as to the presence or absence of gravitational separation, and air from still greater heights had to be provided.

This became possible when some of the 100 odd V-2 rockets seized by the American Army in Germany in 1945 were converted in such a way that instead of the explosive charge they could carry automatic scientific apparatus in the war-head (see Plates V and VI). The successful firing of such a transformed V-2 rocket, which is undertaken at the White Sands Proving Ground in New Mexico, is a very difficult and costly operation, and a smaller, simpler rocket, called the Aerobee, has therefore been constructed in the Applied Physics Laboratory of the Johns Hopkins University [27] (see Plates VII, VIII, and IX). V-2 and Aerobee rockets have lately been used with great success in many different branches of stratosphere research. The devices developed by American scientists for the opening, near the top of the flights, of evacuated metal flasks, and for their closing a few seconds later [28] can be seen in Plates X and XI. The rocket is disintegrated during the flight and the part which contains the flasks is brought down by parachute (Plate XII).

If by these devices a representative sample of stratosphere air has been obtained, the question of its analysis arises. In view of the great rarefaction the analysis may have to be performed on less than a tenth of a c.c. of air, measured at normal temperature and pressure. It is, of course, not necessary to analyse all the constituents in order to find out if a gravitational shift in composition has taken place. It will, however, be very useful to examine at least one which is lighter and one which is heavier than nitrogen because their concentrations in respect to the latter gas must change in opposite directions, and such a fact, if established, would at once rule out several possible sources of error. As mentioned before, we consider the inert gases as by far the most reliable test, since only with them are changes due to chemical reactions completely excluded; the procedure we adopted was to determine in the stratosphere samples the ratios of helium, neon, and argon to nitrogen, and to compare these values with the corresponding ones in ground-level air. From the densities of the various atmospheric gases shown in Table 1, and from Figs. 2 and 3, it is obvious that in gravitational equilibrium the shift should be greatest for the ratio helium : nitrogen; another factor in favour of the helium shift is the high diffusion velocity of this gas which allows it to approach this equilibrium quicker than neon or argon.[29]

However, before we deal with our own experiments a few words have to be said about attempts made earlier in other laboratories to detect a gravitational separation in stratosphere air. All of them were confined to analysis for oxygen. Now oxygen is no doubt the easiest to determine of the constituents of air, but at the same time the most difficult to sample correctly. We are, therefore, very sceptical about a few statements in the literature that at heights below 30 km. a deficit of oxygen has been found. Russian chemists, analysing air from the stratosphere flight reaching 18·5 km., came to the conclusion that the oxygen content was unaltered;[30] but E. Regener[31] claimed that in a sample collected by a pilot balloon from the same height there was already a noticeable decrease in the oxygen content, and he believed that, in the air from a pilot balloon reaching 28—29 km., the percentage of oxygen had dropped from 20·92 to 20·39. However, it appears that even at ground level Regener found slightly less oxygen than the accepted standard figure of 20·95; an examination of his arrangements

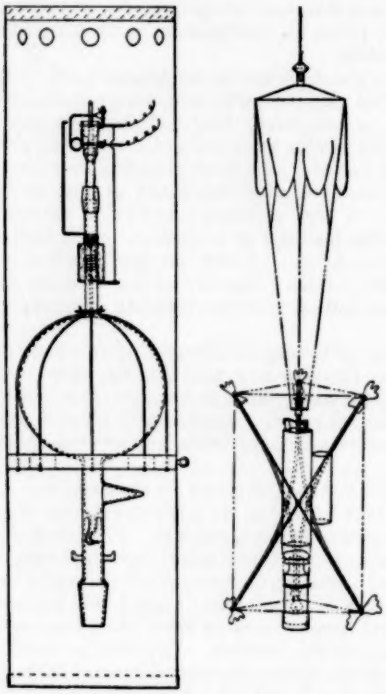


FIG. 5. *Sampling of stratosphere air by sounding balloons. When the rubber balloon bursts, an electric circuit is closed and the tip of the evacuated glass vessel is broken off by the release of a spring. Another electric circuit heats a capillary restriction of the glass tube nearer to the vesse and seals it within a few seconds* (*see ref.* 26). [Reproduced, by permission, from *Proc. Roy. Instn.*, 1937, **29**, 350.]

reveals that the oxygen entered the vessels through a greased stopcock and was then in contact with a clean copper surface. Both grease and copper are known to absorb oxygen even at room temperature, and it is obvious that this effect must become more marked as the quantity of air in the bottle decreases, *i.e.*, the samples from the greatest height must show the biggest deficit. It is likely that the same source of error, to a smaller extent, was operative also in M. Shepherd's analyses of the larger quantities of air brought back from 21 km. by the Americans.[32] There too lubricated taps were used, and it is our experience that they immediately reduce the oxygen content of air by an appreciable amount if the measurements are made with the high accuracy reached by Shepherd. The decisive control experiment, which, unfortunately, does not seem to have been carried out by either Regener or Shepherd, would have been to fill an identical vessel with ordinay air at the same low pressure as that of the stratosphere sample, and analyse it after the same lapse of time.

When, as in our procedure, not the oxygen content but the inert gases are determined, there is a different source of error which has to be carefully watched. Helium dissolves readily in glass;[33] the usual hard glass (Pyrex, Hysil) shows this effect so strongly that its use in an apparatus for sensitive helium determinations is completely precluded but even soft glass, if

previously exposed to air, may give off helium into the vacuum or, alternatively, if it has been carefully degassed it is able to dissolve helium and thus to falsify the analyses in the opposite direction. In the experiments carried out before the last war we sent glass vessels in sounding balloons up to the height of 23 km. and observed slight and irregular increases in the helium content. We were inclined to consider these changes as an indication that from about 20 km. onwards there was a slight enrichment of helium in the stratosphere, but in view of the uncertainty introduced by the glass—which we could not avoid using, in our very lightly built sampling apparatus—we could not be sure, and in our final publication [34] we expressed the view that neither our helium results nor those obtained with oxygen in other laboratories were reliable enough to prove gravitational separation between 20 and 30 km., and that samples from considerably greater heights, and preferably in metal containers, would have to be collected in order to settle the question.

The possibility of obtaining such samples was provided by American rocket research after the war. These rockets can easily reach 70 km., and air is collected in metal bottles; however, the first samples we received were not in the original containers but had been pumped into glass vials. We were not too astonished to find that the helium values did not show the same consistency as those of neon and argon, and that some samples had even less helium than ground-level air (see Table 2). We therefore urged our American collaborators to send us the original steel bottles and our latest analyses were made with samples which right to the moment when we introduced them into our glass apparatus had only been in touch with steel and copper and could, therefore, not have lost or gained any helium. The results of our analyses, which are presented below, will, therefore, be divided into two groups: stratosphere samples from glass vessels and from steel bottles.

Not much need be said here about our methods of analysis as they have been described in a series of papers [35] (see Plates XIII and XIV). After removal of oxygen and carbon dioxide the argon, containing also the insignificant amounts of the other inert gases, is freed from nitrogen by heating it with barium in a steel furnace. Neon and helium, after removal of the heavier gases, are separated by fractional adsorption and desorption from charcoal; their measurement is accomplished by a refined Pirani gauge which permits the determination of a millionth of a c.c. of helium and neon with an accuracy of 1%. Some attention may be given to the oxygen figures in our tables which confirm our previous statement that even cold copper surfaces—the steel bottles are connected with copper tubes and contain copper membranes for the purpose of opening (see Plate XIII)—absorb this gas to an appreciable extent; it can be seen that in several of the samples hardly any oxygen gas was left when the bottles reached us.

Table 2 shows the results of air analyses from glass vials; they can be easily summarized by saying that the neon and argon figures prove the constancy of atmospheric composition. It should be added that a few of the samples were also analysed for neon at the University of Michigan, with the same result, apparatus modelled on the Durham one being used. As regards the height from which these samples came, we have to take into account the fact that in these early experiments the altitude range during which the steel vessels were kept open was rather considerable, and it is, therefore, not easy to say exactly to what heights these experiments

TABLE 2. *Analyses of stratosphere air from glass vials.*

No. of sample	Height (km.)	Date of sampling	Date of first analysis	Ratio to ground-level air: Oxygen	Helium *	Neon	Argon
16A	49·6 to 53·6	2.6.49	4.8.49	0·61	0·96	0·98	1·00
25D	50·4 to 53·3	6.12.49	17.4.51	0·60	0·98	1·00	1·00
15B	53·6 to 57·7	2.6.49	25.7.49	0·12	1·00	1·00	1·01
19D	54·7 to 58·3	21.7.49	6.3.51	0·00	1·01	—	1·01
3B	55·4 to 65·5	27.5.48	1.12.48	<0·02	0·98	0·99	0·99
1B	61·1 to 72·0	9.10.47	4.1.18	<0·02	0·93	1·00	1·01

* Figures uncertain on account of storage in glass.

should be allotted; careful calculations by Professor S. Chapman [36] make it likely that the vessels were filled soon after opening, and that during the further flight air escaped. For instance, the sample 1B should not be taken to represent the composition of air half way between 61 and 72 km. but probably corresponds to the height of only 62·5 km. This point is essential for comparison with the heights shown in the next table.

The experiments reported in Table 3 were all made on air from steel bottles and are particularly interesting because here for the first time changes of atmospheric composition can be

clearly recognized in different samples; they are shown not only by one constituent, but by three simultaneously, and in every case are in the direction predicted. B-15 comes from a height where alterations in the neon and the argon content, if present at all, are still too small to exceed the limits of possible errors by an amount sufficient to make us sure of their reality. The

TABLE 3. *Analyses of stratosphere air from metal flasks.*

No. of sample	Height (km.)	Date of sampling	Date of first analysis	Amount of air (c.c., N.T.P.)	Ratio to ground-level air: Oxygen	Helium	Neon	Argon
B–13	55·56 to 58·18	26.9.51	23.11.51	6·10	0·50	0·998	1·005	1·001
B–15	58·18 to 60·35	26.9.51	18.12.51	4·13	0·01	1·035	1·008	0·996
B–6	64·3 to 67·0	19.12.50	12.6.51	0·338	0·07	1·44	1·08	0·93
B–8	67·0 to 69·6	19.12.50	25.6.51	0·231	0·25	2·02	1·18	0·89
B–9	69·6 to 71·8	19.12.50	9.5.51	0·535	0·03	2·41 *	1·20 *	0·85 *

* Figures corrected for leakage.

helium figure, however, 1·035 instead of 1·000, which has been determined several times—always bracketed between analyses of ground-level air—must be considered as indicating a slight, but real, increase.[37] More convincing still are the next three samples, B–6, B–8, and B–9, collected during the same flight at successive heights. All of them show a marked increase in the helium and the neon ratios, and an equally obvious decrease in the argon ratio. It should be noted that the helium content in bottle B–8 was found to be as much as twice as high as in normal air. Unfortunately, bottle B–9 did not close perfectly and the small leak which we detected in it explains that in spite of the greater sampling height the total quantity of air was considerably bigger than in the two other bottles. This was most likely due to ground-level air seeping in after the flight, and before the bottle was found and the leak stopped by a protective layer of glyptal wax; no leak was apparent in the bottle when we received it; but, when the glyptal was carefully washed off the sealed end of the copper tube, a very small leak was found, of the right order of magnitude to account for the extra air in the bottle. The figures found for helium, neon, and argon in this bottle showed, in spite of this leakage, still very clear deviations from those of ground-level air, approximately to the same extent as those detected in B–6; since it is fairly well known what quantity of air should have been sampled at the height of B–9, we could attempt to correct for the contamination by ground-level air.

[Of the three steel bottles, B–6 opened and sealed perfectly. B–8, so we are informed, may not have opened fully, as the knife was, at the time of recovery, in an unexpected position, but sealed well. Thus to determine the correct amount of air to be expected in bottle B–9, it does not seem correct to extrapolate through the values for B–6 and B–8, as B–8 probably collected a smaller volume of air than it should have done. Instead, it was deemed best to take the amount of air in B–6 as correct, and to calculate the amount of air to be expected in B–9 from a pressure decrease according to the barometric formula, $P = P_0 e^{-mgh/RT}$ where $T = 280°$ K,[38] $R = 8{\cdot}3136 \times 10^7$ cm.^{2}/sec.^{2}/°K, $g = 980$ cm./sec.^{2}, and $m = 28$ (N_2). The temperature 280° K is rather arbitrary, but the final results are not very dependent on the choice.

Correcting the sample volumes for the varying oxygen percentages, we obtain :

	Ht. (km.)	O_2, %	Net N_2 content (c.c.)
B–6	65·6	1·875	0·332
B–8	68·3	6·81	0·215
B–9	70·7	0·7	0·531

If the nitrogen pressure at 62 km. is taken as 1, then the nitrogen pressure at 72 km. will be 0·3077 (from the above formula). From this it is apparent that if the nitrogen volume at 65·6 km. is 0·332 c.c., at 70·7 km. it will be 0·184 c.c. Thus 0·347 c.c. of ground-level nitrogen leaked in.

Since the experimental value of the helium : nitrogen ratio was 1·49, compared with 1 at ground level, we have :

$$1{\cdot}49 = (R_{He} \times V_{70{\cdot}7} + 1 \times V_g)/V_{total}$$

where R_{He} is the true helium ratio at 70·7 km., $V_{70{\cdot}7}$ is the volume of nitrogen from 70·7 km., V_g is the volume of nitrogen from ground level, and V_{total} is the total volume of nitrogen in the bottle.

Whence $R_{He} = [(1{\cdot}49 \times 0{\cdot}531) - 0{\cdot}347]/0{\cdot}184 = 2{\cdot}41$

Similarly, $R_{Ne} = 1{\cdot}20$ (experimental value, 1·07)

and $R_A = 0{\cdot}85$ (,, ,, 0·95)

Further, the assumption that bottle B–8 did not open fully, but collected its sample slowly with the knife stuck across the copper tube and therefore probably yielded air from a greater average height than would be consistent with full opening, seems to be borne out by the helium figure. If the height from which B–8 is assumed to come is increased by 0·5 km. the three helium values are now all on the theoretical line, and the actual nitrogen volume of B–8 also comes much closer to the volume expected.]

These "corrected" figures are entered in Table 3. It need not be emphasized that such a correction is highly unsatisfactory but it is the best we can do at the moment to get the maximum possible information from the small number of analyses available.

Fig. 6 shows the results in graphical form. It can be seen very clearly that the decrease in the argon and increase in the neon ratio, although quite marked, are much less than the increase in the helium ratio, and that is exactly what one would expect. That the neon : nitrogen ratio shows a larger shift than the argon : nitrogen ratio, in spite of the smaller density difference, may be due to the fact that neon, with half the atomic weight of argon, approaches diffusive equilibrium faster.[29].

If we try to make a more strictly quantitative comparison of the shifts found in our analyses with theoretical predictions for still air, it appears that they are approximately of the right mag-

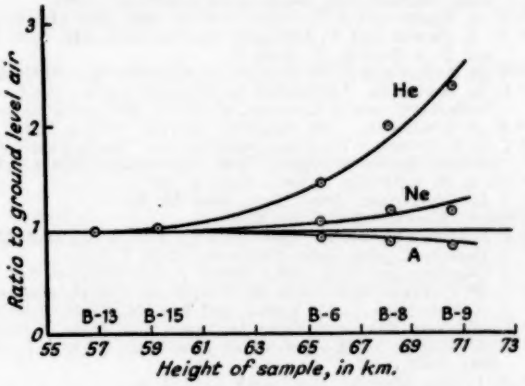


FIG. 6. *Variations in the inert-gas content of stratosphere air between 59 and 71 km.*

nitude. It is too early to draw definite conclusions from these experiments, which are still far too few, but we believe that at present one can summarize our results as follows:

Up to a height of 57 km. no change in the chemical composition of the atmosphere could be detected. In two flights over New Mexico, December 1950 and September 1951, it was found that from about 59 km. onwards the ratios of helium, neon, and argon to nitrogen, changed in a way consistent with the assumption that in this region of the stratosphere gravitational separation is effective, essentially undisturbed by large-scale mixing.

The analyses recorded in Table 3 are, in our opinion, at present the only reliable ones which indicate any variation at all in the composition of the terrestrial atmosphere. So we see that the technique of both sampling and analysing air had to be developed a great deal further since the days when John Dalton climbed Helvellyn and Snowdon and believed that the air brought back in a bottle from some 3000 feet high was poorer in oxygen. The modern results were achieved by the very satisfactory collaboration between the team of physicists and engineers in the University of Michigan who succeeded in obtaining the air samples with rockets, and the chemists in the University of Durham who did the microanalyses of the rare gases. The workers on the American side, sponsored by the U.S. Army Signal Corps, were L. M. Jones, L. T. Loh, H. W. Neil, M. H. Nichols, and E. A. Wenzel; those in Durham, K. F. Chackett, P. Reasbeck, and B. S. Wiborg. The analytical methods have been developed successively in four different University Laboratories, Berlin, Koenigsberg, London, and Durham, and the work done by the Durham group would not have been possible without the previous efforts of their predecessors; it seems appropriate, therefore, to add here the names of those who during the last 25 years in an unbroken tradition have contributed to the development of the techniques now applied in Durham: K. Peters, H. Gehlen, P. L. Gunther, Wm. D. Urry, W. Hofeditz, K. Loleit, E. Gluckauf, and W. J. Arrol.

Many more analyses, and from still greater heights, will be needed before we can hope to obtain a clear insight into the working of gravitational separation in the stratosphere. The present technique for sampling and analysing ought, with some improvements, to be applicable up to altitudes of about 100 km.

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EXTRAORDINARY GENERAL MEETING OF THE CHEMICAL SOCIETY HELD ON THURSDAY, JULY 17TH, 1952, AT 6 P.M. IN BURLINGTON HOUSE.

PROFESSOR R. P. LINSTEAD, F.R.S., Vice-President, was in the Chair.

The Chairman called upon the Senior Honorary Secretary, Professor H. Burton, to read the notice convening the meeting.

The Treasurer, Sir Wallace Akers, then made a statement on the financial affairs of the Society which had made it necessary for the Council to recommend an increase in the rate of the annual subscription, together with certain consequential changes in the Bye-Laws. After an amendment, proposed by Dr. M. A. Phillips and seconded by Mr. C. S. Woollard, had been defeated, the following Resolution, proposed by the Treasurer and seconded by Dr. F. B. Kipping, was carried with two dissentients :

Resolution I

THAT the amount of the Fellow's annual subscription to the Chemical Society be increased to four pounds ten shillings.

The following Resolution, proposed by the Treasurer and seconded by Dr. F. B. Kipping, was carried unanimously :

Resolution II

THAT the Bye-Laws of the Society be altered by deleting the existing Bye-Law 8 therefrom and substituting the following in its place :

8. (i) The amount of the admission fee, if any, payable on election to Fellowship, and the amount of the annual subscription shall be determined by the Council from time to time subject to confirmation by an Extraordinary General Meeting of the Society. Provided that the Council shall have power without such or any confirmation and whenever it may consider it desirable to do so :

(*a*) Either wholly to remit or to reduce the admission fee or to permit its payment by instalments.

(*b*) Either wholly to remit or to reduce the annual subscription payable by any person who has been a Fellow for not less than 40 years.

(*c*) To reduce (by not more than two-thirds) the annual subscription payable by any Fellow who, at the date when such annual subscription becomes payable, is under 27 years of age, and who is willing to forgo the receipt of certain of the publications of the Society issued to Fellows as hereinafter provided.

Provided further that the Council shall have power subject to confirmation by the Fellows in General Meeting :

(*d*) To reduce to such extent and in respect of such year or years as the Council may from time to time determine the annual subscription payable by Fellows resident in any British Dominion, Colony, possession or mandated territory outside the British Isles.

(ii) The amount of the life composition fee shall be such sum as the Council may from time to time determine.

The following Resolution, proposed by the Treasurer and seconded by Dr. G. Baddeley, was carried unanimously :

Resolution III

THAT Bye-Law 10 be altered by deleting therefrom " 25 years of age " and substituting " 27 years of age " in place thereof.

The meeting then concluded.

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